

## THE MANIFESTATIONS OF EPILEPSY.

EPILEPSY; A THEORY OF CAUSATION FOUNDED UPON THE

CLINICAL MANIFESTATIONS AND THE THERAPEUTIC  
AND PATHOLOGICAL DATA.

J.J.M. Shaw, M.A., M.B., Ch.B.

in striking progress of knowledge by modern methods of examination the phenomena of epilepsy, which have remained hitherto obscure, remain to a large extent obscure. Since the first description of the malady by Hippocrates and the accurate and picturesque account of a convulsive seizure by Lucian, very theories of causation have been advanced which have not only remained unaltered, but have been improved in recent years. However, some definite attacks of epilepsy have been observed and studied since the first description of the disease, and the study of the clinical manifestations and the pathological data and the investigation of the heredity of those affected. Although these facts may be comparatively few in number, it is surprising that no attempt is made even in the most recent text-books to correlate such facts as are known and accepted and to formulate a comprehensive theory which could be tested by experiment and further and independent observation.

The observed and verified features of the disease which require correlation are these—

The convulsive seizure or "Grand Mal";

The minor attack or "Petit Mal";

The occurrence in many cases of a warning, mental or sensory in character or an impending convulsive attack termed the aura; also the so-called "psychical" epileptic states of emotional instability and erratic conduct.

The post-convulsive states of stupor, sleep or excitement.

The production of the epileptic phenomena and habit by trauma, gross cerebral lesion and cardio-vascular degeneration (senile epilepsy).

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The production of the epileptic phenomena and habit by trauma, gross cerebral lesion and cardio-vascular degeneration (senile epilepsy).

The regular incidence of fits in many cases, especially during certain stages of sleep, also the occurrence in some subjects of a fit at the inception of sleep called the pre-dormitial fit.

The strong hereditary factor in the disease and its relation to various types of insanity.

The changes of a structural and biochemical type found after death in the cells of the cerebral cortex and in the lymph spaces and capillaries.

The abnormalities of epileptic blood in regard to Alkalinity, Agglutinability, Coagulability and the formed elements.

The changes in relation to the convulsive state in the urine, especially its content of uric acid and phosphates and the occurrence of post-paroxysmal albumosuria and mucinuria.

The effects of various therapeutical substances, in particular the bromides and alkalies.

The benefits derived from the restriction of certain forms of food and especially the Purin bodies.

#### (1) The Convulsive Seizure.

The diagnostic symptom of epilepsy is the occurrence at varying intervals of a sudden loss of consciousness accompanied usually by a strong contraction of all the muscles which pass through a stage of tonic spasm and return by clonic contractions to a flaccid condition. The tonic spasm may be immediately preceded by localised twitchings of the thumb, forefinger and hand, the most animal parts of the body according to Hughlings Jackson. (1)

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- (1). Hughlings Jackson. "Lumleian Lectures on Convulsive Seizures". British Medical Journal, i/90.p.703.



recovery. The sudden re-entry of blood stopped the spasms and in a

Cyanosis rapidly develops owing to the cessation of respiration on fixation of the chest wall and diaphragm. The rate and force of the heart's action may or may not be affected.

It is generally acknowledged that this state is produced by a sudden excitation and discharge of the cortical neurons.

"The function of the nervous system and especially of the cortex of the brain depend on a capacity for the instant release of nerve energy".(1). The regulation of the release of this energy is dependent upon an extremely delicate intermolecular action and transfer of the products of metabolism in true solution and in gaseous form between the cortical cells and the fine capillaries through the perivascular lymph spaces. The epileptic convulsion corresponds closely to the change produced experimentally by local mechanical stimulation or by a sudden cerebral anaemia caused by obstruction of the flow of blood to the cerebral vessels or by stasis or clotting of the blood in the capillaries and small veins. By occlusion of the carotid and vertebral arteries in a rabbit, Astley Cooper at once caused spasm and the cessation of respiration.(2). Kussmaul and Tenner tied the left subclavian and innominate arteries of a rabbit." The immediate symptoms were loss of consciousness and voluntary movement. These were followed in ten to forty-five seconds by clonic spasms beginning in the neck; then occurred dilation of the pupils respiratory gasps at longer and longer intervals and finally cessation of respiration. After complete occlusion of these arteries for not longer than two or three minutes, the brain, on the ligatures being loosened, showed the power of complete

Mandel, 5th Ed., 1911, pp. 250-251.

(4) A.E. Wright, Tissue and Cell Metabolism, Lancet, Feb. 27, 1892.

(1) Sir W.R. Gowers, M.D. System of Medicine (1911) Albutt and Rolleston, Vol. VIII, p. 484.

(2) Astley Cooper, Guy's Hospital Reports, 1836, 1. p. 457.



recovery. The sudden re-entry of blood stopped the spasms and in no case did it cause them".(1). Hill has produced clonic spasms in himself by compression of one carotid artery and states that on sudden compression of both carotids in man the pupils widen, respiration deepens, dizziness and loss of consciousness follow and epileptiform spasms frequently occur.(2).

A similar result follows the sudden cessation of the flow of blood due to local causes in the cerebrum. The production of embolism by the injection of foreign bodies almost immediately leads to stoppage of the respiration and rise of arterial pressure. Most important of all with reference to the post-mortem findings of Mott and Turner to be later described, are the results of the injection into the circulating blood of a quantity of thrombin solution(thrombin is a nucleo-proteid, according to the researches of Pekelharing and Huiskamp)(3), of leucocytes(these contain a large quantity of nucleo-proteid)and of tissue fibrinogen(impure nucleo-proteid)(4), all of which produce sudden intra-vascular clotting. The experiments of Halliburton and Brodie are also worthy of note. These observers prepared a solution of the nucleo-proteid of animal tissues such as the thyroid, thymus and brain by solution in 2% sodium carbonate and distilled water. The injection of this solution into rabbits produced extensive and sudden intra-vascular clotting and death when large injections were made. "Respiration suddenly ceases, the animal makes a few

The lower or spinal motor consisting of the cord, medulla

(1)(2) Leonard Hill, M.D., F.R.S. Allbutt and Rolleston, Vol. VIII p. 23.

(3) A Text Book of Physiological Chemistry, Hammarsten, trans. by Mendel, 6th Ed., 1911, pp. 250 & 310.

(4) A.E. Wright, Tissue and cell fibrinogen, Lancet, Feb. 27, 1892.

(5) Halliburton and Brodie, Journal of Physiology, Vol. 17, p. 135.

(6) Hughlings Jackson, Op. Cit., pp. 703, 755, 821.

stretching movements and dies: there is no dyspnoea. Sometimes after ceasing to breathe for about a minute the animal gives a few breaths more and sometimes resumes breathing normally".

When a weak solution in large amount was injected, salivation and muscular spasm were produced, the respiration ceased and death ensued. The stoppage of respiration was due to the respiratory centres, section of the Vagi having no result. An interesting idiosyncrasy was evinced by Albino rabbits in which even a very large amount of nucleo-proteid produced no effect.

## (2) The Minor Attack.

The minor attack consists essentially of a temporary clouding of consciousness and is not always easy to diagnose, being closely simulated by some syncopal and hysterical affections. In different individuals these attacks may vary from a slight and fleeting giddiness which may pass unnoticed by the patient and his associates for a considerable time to the more severe forms in which there is almost complete unconsciousness attended by slight muscular twitchings, by falling or standing up suddenly or by some unusual and purposeless movement of the legs or arms. It may be accepted that such phenomena differ only in degree from the major attacks in which a larger cortical area is involved.

Hughlings Jackson has divided the loci of the cortical changes into three levels which may be affected independently:

The lower or sensori-motor consisting of the cord, medulla and pons, which regulate simple movements especially reflex.

The middle level which gives rise to muscular spasm consisting of the motor regions of the cortex, viz., the neurons of the Rolandic area and possibly the ganglia of the Corpus Striatum.

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(1) Hughlings Jackson, Op. Cit., pp. 703, 765, 821.

(2) A. Aldren Turner, M.D. Three Lectures on EPILEPSY (Morrison

Lectures on Edinburgh, 1910, p. 25.

(3) J. S. Risien Russell, M.D. Allbutt and Rolleston, Vol. 3, p. 582.

The higher level affecting mentation, consisting of the centres of the pre-frontal lobes, later more definitely placed between the intermediate precentral and prefrontal zones.(1).

Sudden stimulation of these areas of the higher level produces complete loss of consciousness or mere clouding in the major or minor fit respectively.

The tonic contraction of the muscles exhibited in tetany correspond somewhat closely to those of epilepsy. The clinical signs of tetany, the post-mortem changes in the spinal cord and ~~pe~~ ponto-medullary regions and the benefits derived from similar medicinal substances including the bromides, are strongly suggestive of a corresponding sudden discharge of the neurons but confined to the lower level. Tetany is associated not infrequently with epilepsy(10), and in one case in the London County Asylum, Bexley, the "feeling fits", as the patient described the tetanic convulsions, occurred from time to time concurrent with attacks of "grand mal".

A case in which tetany and myxoedema were associated has been described and in this Asylum there is an epileptic who was admitted with well marked signs of myxoedema which improved markedly upon the exhibition of Liquor Thyroidei. The mental symptoms of confusion and impulsiveness in some cases of tetany resemble those of epilepsy. The arrangement of the lymphatic spaces and the calibre of the capillaries in the affected regions in tetany differ from the cortical type, and the known excitants of the condition, especially gastric dilatation, and the relation of the disease to the parathyroid glands distinguish its causative factors from those of epilepsy.

Attacks of "petit mal" affecting the special senses are not uncommon, especially visual impressions, are not and these are referable to the corresponding tracts of the cortex in the same

(1) W. Aldren Turner, M.D. Three Lectures on EPILEPSY (Morrison

Lectures on Edinburgh, 1910) p.25.

(2) J.S. Risien Russell, M.D. Allbutt and Rolleston, Vol.8., p.582.



way as the purely psychical.

### (3) The Aura and Psychical Equivalents.

Closely allied to the minor attacks are the sensory, motor, or psychical prodromata of the convulsion called the aura. Numerous detailed descriptions of these warnings have been made which do not require repetition. They are in many cases a similar manifestation, as was indicated by Herpin in 1857, (12), to the minor attacks which may be considered as aborted or unspread seizures. A different train of symptoms is observable in some cases, and one patient in this Asylum, at the time of his admission twelve years ago when he had very infrequent fits, would inform the attendants of a peculiar feeling of malaise almost a month before the attack. This sensation gradually developed into a headache as the day approached on which the fit was about to occur and a quarter-of-an-hour before the convulsion actually took place he would leave his work in the ward kitchen and carefully lie down on a couch, loosening his neck-tie and collar. With an increase in the number of attacks and advancing dementia he has lost the ability to forecast his fits with any degree of accuracy.

Another patient feels a pain at the vertex for several days before an attack and, as his fits are almost entirely related to the inception of sleep, he sits up in bed for many hours to apply the sensory stimulus which grasping one arm tightly by the other hand produces. A strong hypnotic (Chloral Hydrat. gr. XX., Pot. Bromid. gr. XXX. in one dose) which the patient frequently asks for, is often efficacious in producing sleep without the occurrence of a seizure.

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(1) Herpin, "Les acces incomplets d'Epilepsie", Paris, 1857.

in many such cases a slight focal softening is present which affects I believe that many of the familiar epileptic traits of impulsiveness and violence may have a physical explanation in the loss of sense of well-being and so are in reality the outcome of an "irritability of weakness" in patients who do not recognise in their state the long drawn out warning of a convulsion. The true "psychical equivalents" consisting of bouts of great excitement or depression and hypochondriasis are often relieved by a seizure: in some cases such attacks alternate with convulsions, a state of cheerfulness and rational conduct being exhibited in the inter-epileptoid periods. They correspond in some degree to the irritability and depression shewn by some females, sane and insane in relation to the menses and are due, as I shall endeavour to shew later, to variations in the state of the blood and the metabolism of the tissues.

#### (4) The Post-paroxysmal states.

It is natural, after a sudden and extensive cortical discharge, that and dissociation of the higher from the motor centres, that a recovery should take place asynchronously and a period of automatism and irregular exhibition of voluntary movement ensue. Some cases shew a stupor of exhaustion, others a true sleep from which they can be wakened, while some shew no such effects but rise and go their way almost immediately after the cessation of the clonic spasms. In several cases I have produced a marked abbreviation of the post-convulsive state by the exhibition of Ammonium Oxalate and Oxalic acid in small doses which I shall later describe.

#### (5) Traumatic Epilepsy.

Following severe injury to the cortex, and, in some cases, cranial injury without gross brain lesion, convulsions may occur which bear an exact resemblance to the so-called idiopathic type.

In many such cases a slight focal softening is present which affects the nutrition of the surrounding areas by derangement of the fine capillary network. In the same way a tumour will cause local vascular changes in addition to a general increase of pressure. The growth of a tumour within the cranium may produce compression of the cerebral capillaries. The cranial contents cannot be increased and if the quantitative ratio of cell tissue to blood vessel be altered it must be at the expense of the blood volume".(1). Senile thickening and irregularity of the vessel walls similarly tend to impair the uniformity of the blood supply from arteries to arterioles and from arterioles to capillaries and so magnify the effect of a slight anaemia of postural or cardiac origin.

#### (6) The Time Incidence of Convulsions.

Many exhaustive analyses of the incidence of the major and minor attacks have been made by different observers and these correspond closely when the averages of large series of cases are taken. Four groups may be conveniently distinguished:-

those in whom the major and minor attacks occur at any hour of the day or night;

those whose fits are entirely diurnal or nocturnal;

those who are liable to attacks only at certain times in their daily routine: such are the post-prandial and predormital convulsions;

those in whom the fits occur cyclically, the paroxysmal bouts being separated by periods of quietude in some cases of several months.

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(1) Leonard Hill, op. cit. p. 34.



### (7) The Hereditary Factor.

With the growing appreciation of the significance of heredity in all forms of insanity and the accumulation of statistics, remarkable evidence is afforded of the relationship between epilepsy and various forms of mental disease. This connection is further shewn by the presence in many lunatics *sae sane* and insane epileptics of the usual stigmata of degeneration and teratological anomalies of the cortex of the lunatic. From observations which I have made upon the blood in epileptics I believe that a condition exists therein which is the exact antithesis of that described by Addis in haemophilia.(1). In this connection the hereditary nature of haemophilia is of interest. In appendix B will be found the hereditary tables of six cases from the records of Bexley Asylum.

### (8) Cerebral Pathology.

Although many cellular degenerations and local scleroses have been described, there are very few changes in the cortex or basal ganglia which can definitely be delimited as epileptic. Similar changes may be found on the one hand in the brain of all patients subject to sudden and recurring seizures such as General Paralysis of the Insane and, on the other, in the subjects of imbecility with which epilepsy is often associated.

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(1) T. Addis, Quarterly Journal of Medicine, Vol.2. No.6, 1909

p.28, etc.

(2) E. Lewis, Textbook of Mental Diseases, London, 1898.

(3) A. F. Campbell, Journal of Pathology and Bacteriology, Vol.2 1896.

(4) Clark and Prout, American Journal of Insanity, 1903-04.

(5) John Turner, M.B., The Pathology of Epilepsy, British Medical Journal, March 8th, 1905.

The vacuolation of the nucleus in the cells of the second cortical layer which was described by Bevan Lewis (1) and upon which he laid much stress, has been shewn to be an inconstant feature in epilepsy and also to exist in other conditions such as tuberculosis and pneumonia(2).

Disappearance of the intranuclear reticulum and its replacement by a fine irregular granular deposit has been described by two American observers(3) and confirmed by Turner(4), by whom a large number of important changes have recently been described. Turner considers that this granular change is preceded by an enormous bladder like distension of the nucleus forming the acute stage. He has found a similar condition in the cortex of a dog after ligation of the cerebral arteries and holds it as evidence of the occurrence in epilepsy of sudden stasis in the cerebral capillaries.

The deepest layer of the cortex, which shews a yellowish-red appearance on fresh section indicative of a slightly greater vascularity than that of the strata external to it, has been termed the polymorphic layer. The cells are rich in nucleo-proteid and in this layer and the small pyramidal layer immediately superjacent, the dendritic processes are believed to be actively amoeboid. the perivascular lymphatic spaces are comparatively large and the cells are freely bathed in lymph. In a case of organic dementia in this Asylum in which the seizures closely

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- (1) Bevan Lewis, Text Book of Mental Diseases, London, 1889.
- (2) A.W. Campbell, Journal of Pathology and Bacteriology, Vol. 2 1894.
- (3) Clark and Prout, American Journal of Insanity, 1903-04.
- (4) John Turner, M.B., The Pathology of Epilepsy, British Medical Journal, March 3rd, 1906.

simulated those of epilepsy in the nature of the spasm, extreme cyanosis, remission by clonus and rapid recovery, a narrow irregular stratum of reddish-yellow and yellow softening was found post-mortem, involving only the deepest cortical layer and, to a slight extent, the underlying white matter in small areas. The cortical layers external to the line of Baillarger presented the usual grayish colour. These lesions were found in the right motor and left frontal areas.

A similar narrow strip of advanced softening was found in another case with sudden convulsions but in this brain there were also softenings in the right Corpus Striatum. The blood vessels of the cortex which arise from those of the investing Pia Mater run more transversely in the inner than in the outer cortical layers. The lymph spaces are formed chiefly of fine processes of pial membrane and the usual trabeculae, visible in the other regions, are not seen in the cortex.

Sclerosis of the Hippocampus Major which is commonly found in epilepsy has been thoroughly investigated and described at great length. It is not now considered in the light of a causative factor(1) and Turner attributes it to occlusion of the nutrient vessels.

Mott has demonstrated micro-chemically that biochemical changes occur in the cortical neurons at temperatures of  $105^{\circ}$  and  $106^{\circ}$  and also after epileptic fits even without pyrexia. He states that the observed changes are not due to exhaustion but to an altered chemical condition of the lymph in which the cells are bathed.(2). He also states that the congestion and stasis of the vessels along with oedema of the brain, inasmuch as it is contained in a closed cavity, must be associated with a corresponding arterio-capillary anaemia.(3).

(1) Ford Robertson, Pathology of Mental Diseases, p. 186.

(2), (3), F.W.Mott, Archives of Neurology, Vol.1. pp. 494 and 499.



The changes in the pia-arachnoid membranes do not call for detailed description. The most important observations are those of Turner who has found in the lesser vessels of the membranes changes similar to those in the cortex. (1).

There is no marked thickening of the walls of the smaller cortical vessels. The perivascular lymphatic spaces are dilated. Sir James Barr states that the size of the capillaries of the body varies from 7 to 13 micromillimetres. (2) In the cortex, although Ford Robertson gives 4 micros as the minimum of fineness, Turner states positively that he has found capillaries of from one to two micros, in passing through which the erythrocytes become elongated. (3)

Several observers including Professor Osler have shewn that blood plates in aggregated masses cannot pass through capillaries. Turner finds many indications that stasis in the smaller vessels is produced in a great degree in epilepsy and to this condition, suddenly effected, he attributes the rapid anaemia which results in a convulsion. The general congestion which is recorded by all observers is due to the engorgement of the capillaries and small veins, the arterioles being comparatively empty. Associated with the congestion Turner has observed numerous petechial haemorrhages scattered throughout the cortex and small angiomas have been observed. (4). Turner attributes the dilatation of the capillaries in status epilepticus to a compensatory rise of blood pressure to overcome the distal blocking by masses of the formed

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(1) John Turner, M.B. Clinical Study of Epilepsy, Aldren Turner.  
Chapter on Pathology, p. 170.

(2) Sir James Barr, M.D. British Medical Journal, Aug. 31 1906.

(3) John Turner, M.B. Journal of Mental Science, Oct. 1908, p. 648.

(4) Drysdale J.H., Transactions of Pathological Society, London,  
1904, p. 72.

elements. Spheres composed of agglutinated blood-plates (containing phosphorus and thus indicating their nucleo-proteid origin) are found lying in the capillaries, also hyaline casts formed by a complete fusion of the platelets, granulated debris, and in rare instances, threads of fibrin.

I have found and will later describe a tendency in the blood of epileptics to abnormally rapid agglutination with comparative slowness in the formation of a true retractile clot; this is in harmony with these post-mortem observations.

A condition which Turner emphasises is the presence of a sticky exudate in the sub-pial space which, he states also exists in the communicating perivascular spaces. In almost all the cases of General Paralysis in which there has not been actual adherence of the membranes to the brain, I have found a similar sticky exudation. It is most commonly found in rapid cases and in those in whom seizures have been absent or infrequent, and I regard it as the first stage in the adherence of the membranes. Combined with a granular wasted appearance of the summit of the convolution I have also observed it in three epileptic brains.

Contradictory observations have been made upon the composition of the cerebro-spinal fluid especially as to the presence of Cholin. It may be accepted that there is no pronounced deviation in composition from other congestive and seizural states. Cholesterolin is commonly found and the important observation has recently been made that the carbonates, uric acid and lactic acid may also be present. (1)

#### (9) The Blood IN Epilepsy.

In recent years the physical and chemical abnormalities of the blood have been the objects of much research. The conditions which I shall describe at present, like the other matters treated in these sections, are intended to take places in a large

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(1) W. Mestrezat, Le Liquide Cephalo-Rachidien, Normal et Pathologique. Paris, 1912, p. 407.

series of premises from which a conclusion can later be drawn and, as I believe the morbid factors in the blood to be of great importance in the production of the convulsive and minor attacks and in relation to treatment, I shall deal with them along with some relevant healthy conditions.

The reaction of healthy blood is very slightly alkaline and that of the serum when the alkali protein compounds in the formed elements are eliminated, is practically neutral.(1).

The blood corpuscles give up a part of this alkali united with protein to the serum by the action of carbon dioxide, hence the serum becomes more alkaline.(2). The addition of carbon dioxide of course decreases the total alkalinity.

The alkalinity changes transitorily after absorption of some foods and may be altered by the exhibition of acids and alkalis. It presents however, a regular diurnal variation, being low in the morning, high throughout the day and falling again in the evening.(3). The total reaction may actually become acid in cases of uraemia, ~~diabetes~~ diabetes and cholera.(4),(5). In one case of diabetes the amount of acid per kilometre was equivalent to 1.75 grammes of H.Cl. These changes imply a considerable degree of acidity of the serum.

The researches of Charon and Briche(6) upon the reaction of epileptic blood shewed that the seizures occurred in inverse

The drainage after the fit is due to the chemical and

(1) L.Henderson, American Journal of Physiology, 1908.

(2) Hammarsten, op. cit. p. 298.

(3) Hunter, R. Recent Advances in Haematology, p. 4.

(4) Sahli Diagnostic Methods, trans. by Potter, 1911 p. 736.

(5) Emerson, C.P., M.D. Clinical Diagnosis, 2nd Edit. p. 546.

(6) Aldren Turner, Epilepsy, 1907, p. 194.

Pugh finds that the administration of bromide salts at first



relationship to the degree of alkalinity, the minimum frequency of the attacks corresponding to the maximum blood alkalinity and vice versa. The conclusions of Pugh(1) in relation to the final issue of this thesis are of sufficient importance to be quoted in full.

" The average alkalinity of the blood in the inter-paroxysmal states is lower than the average of the control cases.

The diminution is gradual and progressive and is more marked in cases suffering from gastric catarrh and constipation. There is a marked sudden and pronounced fall immediately prior to the onset of a fit.

There is a further fall in alkalinity after the fit is over; this diminution is seen in from three to ten minutes after the attack.

This after diminution depends on the duration and severity of the muscular twitchings and upon the degree of inter-paroxysmal alkalinity.

There is a gradual return of the blood to its normal alkalinity which takes place in five to six hours, the rise being more marked in the first hour.

If the alkalinity keeps at a low level it may determine the onset of another fit.

The diminution after the fit is due to the chemical end products of muscular metabolism, i.e., sarcolactic and carbonic acids and not to substances in direct relation to epilepsy.

The diminution after the nocturnal fit takes a longer time to return to the normal than the diminution after a day fit."

Pugh finds that the administration of bromide salts at first

(1) R. Pugh, M.D., Brain, 1902, p. 500.

raises the alkalinity but this is not maintained even with increased dosage, thus indicating that the bromides must have another means of controlling the convulsive states than by merely affecting the alkalinity.

The metabolism of the tissues depends upon a certain degree of alkalinity of the circulating fluids and it is essential for the activity of the cortical neurons. As a result of metabolism, acid products accumulate among which are lactic, carbonic and uric acids and urea. Uric acid is derived from katabolism of nucleo-proteins. It is found, along with the purine bases, choline and paralactic acid, as an extractive body in the normal brain(1)

The Viscosity of the blood is dependent upon two factors-the number of the formed elements and the quotient of carbon dioxide, being high when the corpuscles are increased and when the blood is rich in carbon dioxide.(2).

The viscosity increases during narcosis according to the depth of the sleep.(3).

The increase in viscosity is a stage in the development of agglutination and coagulability, and viscosity increases in degree according to the reduction in the alkalinity. Dastre and Floresco(4) have found that non-coagulable peptone plasma is alkaline and that it loses its non-coagulability if rendered neutral or faintly acid. Emerson finds that the alkalinity rapidly diminishes till coagulation is effected and then it remains almost constant.(5).

(1) Hammarsten, op.cit., p. 576.

(2) Hammarsten, ibid., pp. 298, 386.

(3) R. Burton Opitz, Journal of Physiology, No. 32.

(4) General or Experimental Pathology, W.S.Lazarus Barlow, M.D.

2nd Edit. 1904, p. 142.

(5) Emersoe op. cit. p. 546.

As an intermediate stage between the highly viscous but still fluid blood and coagulation with the formation of a retractile clot and serum exudation, comes agglutination. The mechanism of agglutination which is probably of greater importance clinically in the development of stasis and thrombosis than coagulation, has been only partially studied although its importance was recognised by Hunter in 1873. It may occur in defibrinated blood and so is not dependent upon fibrin formation. Addis(1), finds that the first appearance of slight stasis is too rapid and variable a feature in a suspended drop of blood to be taken as a determining point in the estimation of coagulation. Such a stasis, however, would be of the greatest importance in the network of capillaries especially in the cerebral cortex. It is probably due to a simple cohesion of the corpuscles in the presence of the highly viscous blood plates before and during their interaction with prothrombin to form thrombin which eventually acts upon fibrinogen transforming it into fibrin.

In relation to the discoveries of MacCallum and Voegtlin(2) regarding the calcium content of the blood in experimental tetany, I made preparations to estimate the calcium content in epileptics by Wright's method. ~~Wright~~ (3) This consists of the estimation in a long fine capillary tube of the concentration of Ammonium Oxalate which permits and that which inhibits coagulation in a series of dilutions, and so the quantity of calcium in parts per 1000 of blood. After some practise, the method worked easily and well and I obtained uniform results, using my own blood and that of six non-epileptic patients whom I intended to use as controls. In none of

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- (1) T. Addis, Quarterly Journal of Experimental Physiology, Nov. 1908  
 (2) MacCallum and Voegtlin, Journal of Experimental Medicine, 1909.  
 (3) Sir A.E. Wright, M.D. Technique of the test and capillary glass tube, 1912, p. 85.



to maintain the thread like shape of a clot but broke up in these instances was there the slightest difficulty in intermixing the drops of blood with the dilutant on a glass slide and drawing them up into the long capillary tube. I then proceeded with the same apparatus and solutions to apply the method to my epileptic cases, but was surprised on the first trial to find that only five out of the thirty two dilutions in the four cases would enter the tubes, agglutination having taken place almost immediately. On continuing these investigations upon my other cases (~~2516~~ Appendix Ck) I found the same phenomena in nearly every instance which rendered the method entirely inapplicable to epileptic blood, so far as the calcium content was concerned, but extremely interesting as regards the agglutinability. A much deeper stab was required to produce a sufficiency of blood in the epileptic than in the non-epileptic cases and the flow ceased very quickly. I believe the abnormality to be due in part to an excessive and readily accessible quantum of thrombokinase in the injured tissue cells of the wound and to a ready disruption of the polymorph leucocytes and liberation of the thrombo-kinase content of the blood plates. I attempted to estimate the comparative times of agglutination in different cases by placing a series of drops on a slide and taking the earliest time at which a drop could not be drawn into the capillary tube as end point. As, however, the differences were matter of seconds and depended largely upon the rate of flow from the wound I could not obtain reliable or constant results or estimate the relation to convulsions, but I attached great importance to the general greatly increased rapidity in agglutination in epileptic compared with non-epileptic blood.

In contrast to this rapid agglutination, I found the formation of a true retractile clot very rare in those specimens of blood which did enter the tube even when mixed with the weakest dilutions of Ammonium Oxalate. A simple sedimentation and cohesion of the corpuscles occurred which, on expression into water failed

to maintain the thread like shape of a clot but broke up in granules or disseminated in a fine pinkish cloud.

In the presence of the chlorides of sodium and, more strongly of calcium a true clot with exudation of serum between the thread of clot and the walls of the tube, was visible and this maintained its form when expressed into water like a clot from normal blood undiluted or in the low dilution of oxalate.

It is highly probable that this rapid agglutination may have vitiated the results of observers who have removed the blood direct from the wound into capillary tubes and who have found the coagulation time unusually rapid in epilepsy; so far as I am aware the coagulation time in epilepsy has not been estimated by the recently devised oil impingement method of Addis. Addis described a similar sedimentation and agglutination in the majority of bacterial diseases, typhoid being a marked exception, and in uraemia, acute nephritis and cirrhosis of the liver; he quotes the opinion of Flexner that this agglutination may be a source of thrombosis in disease. (1).

Turner found a considerably reduced coagulation time in the periods immediately before and after the convulsive attacks as well as a general reduction in the inter-paroxysmal periods (2). These results, in view of the relation which has been mentioned between reduced alkalinity and coagulability, are in accord with Pugh's observations upon the reaction of the blood in epilepsy.

#### The Cellular Elements.

No pronounced change has been observed in the number or character of the erythrocytes in epilepsy, but numerous variations in the leucocytes have been recorded. Contradictory statements have been made regarding the total leucocyte count. Lewis Bruce finds a persistent hyper-leucocytosis, more marked after the

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(1) T. Addis, Edinburgh Medical Journal, July 1910, p. 47.

(2) J. Turner, M.B. "Thrombotic Origin of Epileptic Fits" Journal of Mental Science, Oct. 1908.

paroxysmal periods, when it may rise to 30,000, a result which he attributes to toxæmia.(1)

J. Turner states that a considerable leucocytosis is usually present, but has not observed any marked variation in the paroxysmal period(2). McPhail found a leucopenia of 20% below normal which altered to normal on the administration of bromides(3).

Pugh(4) has found a constant increase in the leucocyte count after convulsion, the increase being due to the small and, to a less extent the large hyaline cells. The polymorphonuclear cells are diminished. The degree of leucocytosis is not so marked in status epilepticus and is diminished with each seizure.

My own observations( Appendix D) conform to those of Pugh in the differential counts, but the total numerical variations before and after seizures were not greatly marked. I also failed to find what could be called a hyperleucocytosis in any case in the inter-paroxysmal period, the maximum of 28 cases being 15,800, the minimum 7,600, and the average between 10,500 and 11,000.

The blood changes at the convulsive periods are of great interest, like the hypo-alkalinity, in relation to the hypothesis of cortical endo-vascular stasis and agglutination.

According to the views of Schmidt and the Dorpat school(5) an abundant destruction of leucocytes, especially polymorph, takes place on coagulation. I have examined on several occasions agglutinated blood by compressing it between cover slips and staining, and also the soft agglutinated masses of corpuscles which form

is the quantity of -----

(1) Lewis Bruce, 8 Studies in Clinical Psychiatry, 1906, p. 169.

(2) Aldren Turner, "Epilepsy" p. 193.

(3) McPhail, Journal of Mental Science, 1884, Vol. xxx.

(4) Pugh, "Brain", 1902.

(5) Hammarsten, op. cit., p. 301.

(1) J. Turner, M.D., B.N.S., M.R.C.P., 1904.

(2) Gulland and Gossell, The Blood, p. 157.

(3) Hill and Widdarsh, Proc. of Phys. Soc., 1905.

(4) Aldren Turner, op. cit., p. 193.



the so-called post-mortem clot. In both conditions, although the leucocytes have lost their affinity for basic dyes to some extent I have found a comparative diminution in the number of polymorph cells. Some investigators believe that there is no actual disintegration of the polynuclear cells but merely an elimination of their contents, a process called 'plasmolysis' by Lowit.

The blood plates, with which I shall deal later as an important nucleoprotein containing element, are said to be considerably increased in the blood after convulsions and have been found in agglutinated masses in the cerebral capillaries. (1)

In cases of chlorosis in which the blood platelets are increased in number it is said that a special tendency to venous thrombosis exists and, in some of these cases long cylindrical masses of plates, probably washed from the capillaries, can be found in the film. (2)

The gaseous changes in the blood in epilepsy have not been greatly studied, but it has been found (3) that in epileptiform fits provoked in animals by the injection of the essential oil of absinthe, a much greater increase takes place in the Torcular Herophili than in the femoral veins and carotid artery.

#### (10) The Urine.

Closely allied to the variations in the reaction of the blood are the changes in the uric acid output in the urine. A diminution in the quantity of the uric acid in the urine passed before a convulsion and an increase in the first quantity passed after it has been generally observed (4) and examinations which I have made support this observation. This change is not observable to the same degree after minor attacks. I have also found an almost

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(1) J. Turner, M.B. B.M.J., Mar. 3rd. 1906.

(2) Gulland and Goodall, The Blood, p. 141.

(3) Hill and Nabarro, Proc. of Phys. Soc. Mar. 16th 1895.

(4) Aldren Turner, op. cit. p. 189.

ge thus--

ases uric acid etc.

attacks as the sole criterion of treatment is, however, becoming increasingly discredited. That bromides may have a depressing effect and may produce serious symptoms in those who require more than a small dose is well recognised. I have found that many patients prefer even a considerable number of fits along with a proper sense of well-being in the intervals to the bromide effects of impaired appetite and lessened mental and physical efficiency. One must remember however, that the serious contingencies of convulsions are obviated to a great extent in institutions by suitable work and play and by continuous observation of those who may be injured by a sudden fall. Belladonna, an old remedy, is still used, and digitalis is a useful adjunct to treatment in a few cases.

The alkalies, especially biborate and carbonate of soda, have been proved to be useful, and I found in several cases great improvement resulting from the latter. In one female ward in which I gave it a trial, the patients in a short time became more tractable and cheerful and in three cases commenced to do ward work for the first time. It came to be known in the ward as the "good temper medicine", and one of my colleagues, impressed by its reputation in this epileptic ward, tried it widely among his non-epileptic patients but with absolutely barren results.

From the exhibition of Oxalic Acid and Ammonium Oxalate in  $\frac{1}{2}$  grain and 1 grain doses respectively, I have received most gratifying results in certain cases. In several instances a marked diminution in the number of convulsive attacks and a great diminution in the attacks of petit mal have taken place. While they are less effective in controlling the major attacks, in the small doses in which I gave them, than the optimum dose of bromide, I believe that they are more effective in diminishing the minor attacks. In some cases I gave Oxalic Acid gr. 1, before breakfast and ten or fifteen grains of Ammonium Bromide at bed-time with very good results. But more important than its action upon the



convulsive attacks has been its effect upon the patient's mental condition and the curtailment of the post-seizural depression and confusion. One case who has been on bromide almost continuously since his admission twelve years ago (except in the recent control state in which he had no medicine), and was known to exhibit regularly a post-seizural phase of stupor followed by restlessness and impulsiveness lasting from one to four hours succeeded by headache, -this patient after the first fit since the inception of the oxalic treatment, a period of four days, rose in four minutes from the cessation of clonus; walked unaided to the ward from the bath room, where he was at the time of the fit, and commenced his work as boot cleaner. This marked curtailment of the post-paroxysmal state has been evident now, without exception, for seven weeks.

I have not relied upon my own judgment alone in estimating changes upon the patients, but have also taken the opinions of the different attendants who have known the cases over long period. I carefully refrained from expressing an opinion about the effect expected from the different substances which I ordered in the wards: at the same time I was prescribing several medicines which turned out to be ineffective or deleterious about which I received free expressions of opinion from patients and staff and so their statements were of considerable value.

To avoid obscuration of the central idea of this thesis I have placed the details of my oxalic treatment and of the other substances which I used in Appendix G.

I will only mention here that the administration of the glycerophosphates, including Calcium glycerophosphate, Phytin Liquidum and Sanatogen, produced deleterious effects, both the frequency and the severity of the seizures being increased. I obtained no pronounced effects from the exhibition of the emulsion of Lecithin nor from the calcium salts, but such as were produced were bad. Calcium Bromide is inferior to the other bromide salts in common use.

hagball institution, has observed benefit from an operation in  
(12) Dietetic treatment. is drained by puncture of the soft

It is generally accepted that a diet rich in meat is more prejudicial in epilepsy than a farinaceous diet. (1) Turner quotes the opinion of Alt that a diet without meat is the most satisfactory. More recently De Fleury has recommended a strictly vegetable ~~diet~~ diet with the suppression of all foods of animal origin including milk. (2)

A purin free dietary has been strongly recommended by Turner and has received fairly general approval. (3) The purin bodies are present in a large number of foods including the white and red meats and are decomposition products of the nucleoproteids.

A salt free dietary, first recommended by Hughlings Jackson, has been widely tried and has been found a useful adjunct to the administration of bromides. A great success has been claimed for it at the Massachusetts Hospital (4). In three out of four cases in which I added two drachms of salt daily to their usual quantum no effect was produced. In the fourth case a marked increase in the number of fits occurred and he exhibited a marked diuresis, passing on one occasion 130 ozs. of urine in twelve hours. This fact is interesting in view of the statement of Straub and Rost that if the increased ingestion of salt is accompanied by diuresis which is not compensated by drinking water, a rise in the protein metabolism occurs (5). failed to support his findings.

The presence of an organism which he called the 'neurococcus' has Operative interference has not produced good results in many cases. It has recently been advocated by Alexander who, at the

(1) Aldren Turner Epilepsy, p. 244. approved (4). Gowers says

(2) De Fleury, Journ. des Practiciens, Oct. 1912 Review, B.M.J.

Alexander, M.D. 12 Nov. 30th, 1912.

(3) Aldren Turner Practitioner, 1906.

(4) A Morton, Boston Med. & Surgical Journal, 1903.

(5) Hammarsten, op. cit. p. 863. and Bull. 1901, p. 28.

Maghull Institution, has observed benefit from an operation in which the sub-pial space is drained by puncture of the soft membranes and fenestration of the dura mater(1). In these cases he has found an excessive oedema of the pia-arachnoid membranes and excess of sub-pial fluid which is clear sterile and of the constitution of dilute lymph.

produced in some cases of scarlet fever in the eliminatory cells of the choroid plexus, comparable to the changes in the renal epithelium, is instructive and may account for the morbid changes in the cerebro-spinal fluid in such cases.

Three propositions which have been advanced to explain the phenomena of the disease but do not appear to me to come within the category of accepted or proven fact, require mention and elimination. They are-

The Microbic,

The Purely Toxic,

The Cardio-vascular Theory, supported

especially by Dr. A.E. Russell.

Dr. H.M.Greene of Portland, Oregon, states that he has observed the presence of a large diplo- and small micrococcus in two specimens of the blood of a case of epilepsy following scarlet fever, and also in another idiopathic case without a known toxic or febrile origin(2). He reports that he managed to prepare a valent vaccine from these ~~specimens~~ bloods, but further observations during twenty years have failed to support his findings.

The presence of an organism which he called the 'neurococcus' has been described by Bra and discredited by other observers who shewed it to be the creation of faulty technique(3).

That a large number of cases date their origin from an attack of scarlet fever has been generally approved(4). Gowers lays

(1) W. Alexander, M.D. Lancet, Sept. 30th, 1911.

(2) H.M.Greene, Lancet (Review) July 22nd, 1893.

(3) Aldren Turner, Epilepsy, <sup>p. 196.</sup> 2nd Edit. 1901, p. 28.

(4) Sir W.R.Gowers, Epilepsy, 2nd Edit. 1901, p. 28.



stress on the fact that the toxins of the disease give rise to chemical changes in the nervous system, as shewn by the frequent occurrence of optic neuritis as a sequela. Influenza has a similar but less marked effect in provoking epilepsy. The speculation that deleterious effects may be produced in some cases of scarlet fever in the eliminatory cells of the choroid plexus, comparable to the changes in the renal epithelium, is instructive and may account for the morbid changes in the cerebro-spinal fluid in such cases.

Inclusion bodies in the polynuclear leucocytes, of similar appearance and reaction to some which I will later describe, have recently been observed in excess in scarlet fever(1).

A microbic origin is not in accordance with the nature of the disease. It bears no relation to successful although admittedly empirical treatment, and it receives mention but no support in modern literature.

Although various toxic substances, especially cholin(~~4030ms~~) (various observers) and carbonic acid(Krainsky), have been described as the direct cause of convulsions, their actual causative nature has been found experimentally defective and the strong balance of opinion places them as a resultant and not a provocative change in relation to the paroxysms.

A large mass of evidence has been adduced by Dr. A.E. Russell in support of the theory of causation by cardio-vascular insufficiency and in a much less conclusive way, by arterial spasm in the cerebrum. He maintains that the difference between faint and epileptic attack is a difference in the degree and not the kind of cerebral anaemia and the different rate of development(2).

(1) Nicoll and Williams, Archives of Pediatrics, May 1912.

(2) A.E. Russell, Lancet, April 3rd. 1909. Med. Sect. 72.

"In the ordinary faint the cerebral circulation slowly diminishes *pari passu* with the falling blood pressure. In the fit there is sudden cessation of the circulation. In the faint the circulation slowly improves: in the fit it returns with greater rapidity". Stress is laid on the fact that loss of consciousness may precede convulsions(1). He quotes three cases of Gowers' in which syncopal attacks in childhood have passed into epileptic attacks in adult life, and also three of Moxon's in which epileptiform attacks followed an arrest of the heart's action which he attributed to vagal inhibition. Russell states that the pulse irregularities are great and the vaso-motor system unstable in epileptics.

While readily accepting the statement that a sudden cerebral anaemia produced by cardiac or vaso-motor change may be the cause of epileptiform attacks, as best shewn in the phenomena of the Stokes-Adams syndrome in which bradycardia and arrhythmia are always present, the evidence that this is the usual or even a rare cause of idiopathic epilepsy is wholly insufficient. Even admitting that a vaso-motor or cardiac instability is present in some cases, Russell fails to shew any form of sudden excitant of the attacks except by an analogy with the Stokes-Adams syndrome where an extreme type of circulatory disorder obtains.

In the discussion which followed a lecture by Russell on the Pathology of Epilepsy(2) in which he upheld the cardio-vascular theory, the post-mortem results of Leser were adduced in opposition to Russell's arguments. Leser found in 500 epileptics that 1½% had signs of heart disease, and in 800 diseased hearts not 1% were epileptic. Aldren Turner has found valvular disease of the heart in 1.8% of his cases.(3).

The results of three observers in a number of cases shew that there is no considerable change in the rate or amplitude of the

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(1) Russell, Lancet, April 10th, 1909.

(2) Russell, Proc. of Royal Soc. of Med. i. Med. Sect. 72.

(3) Aldren Turner, Epilepsy, p.164.

pulse until the clonic state is reached and no sudden lowering of blood pressure occurs. They agree that the cause must be a local one in the brain rather than a sudden fall in pressure from cardiac inhibition or splanchnic dilatation(1).

The fact that the pulse rate may be slightly reduced and may occasionally become irregular during the clonic spasm is of not necessarily of importance if we consider the degree of muscular pressure which is exerted upon the blood vessels during a contraction. As a rule the frequency and force increase at this stage(2). In examination of the fundus oculi by the direct method from before the commencement of the fit to the end, Gowers has not detected in any of several cases the slightest change in the size of the vessels(3). This serves to contradict the purely speculative theory of arterial spasm, and, indeed, the presence of vaso-motor nerves in the walls of the cerebral vessels has not yet been conclusively demonstrated(4) (5).

With a view to determining the degree of the alleged vaso-motor instability in epileptics I have made fairly comprehensive observations upon the pulse mobility, the blood pressure, tache cerebrale, capillary pulsation, the state of the heart and vessels and the soundness of sleep in epileptic and non-epileptic cases. (Appendix H). The total result is to shew a very slightly greater degree of instability among epileptics, chiefly in the senile cases but quite insufficient in my opinion to be a causal factor in the disease. Following a major attack, the instability, in company

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(1) A.G. Gibson, T.S. Good and R.G. Penney, Quarterly Journal of Medicine, 1910, p. 5.

(2) Gowers, Epilepsy, p. 107.

(3) Ibid. p. 107.

(4) Leonard Hill, System of medicine, Allbutt and Rolleston, Vol. 8, p. 10

(5) Ford Robertson, Pathology of Mental Diseases, p. 298.



with that of other functions of the body, is naturally greater. The cases which I took were all upon the same dietary and were induced for exactly the same number of hours per night. The general state of sleep among epileptics appeared to be deeper than in non-epileptics. demonstrated in the fall in alkalinity prior to a convulsion and the general incidence of the convulsions in relation to the alkalinity of the blood.

Between the foregoing critical analysis of the conditions which obtain in Epilepsy and the second part of this thesis in which I shall endeavour to substantiate a correlating theory of causation I will, for the sake of clearness, interpose a brief statement of the conditions which I believe to be responsible for the epileptic manifestations.

The convulsive and minor attacks in epilepsy are produced by a sudden cerebral anaemia, due to a temporary stasis of the circulation in the cerebral capillaries and small veins, which is removed at once or by degrees, by the rise of blood pressure which occurs when stasis has been effected. The actual convulsion may be preceded by an aura due to increasing viscosity and developing stasis of the formed elements of the blood and may be succeeded by a period of irregular cortical excitation as the agglutinated elements are removed from the fine capillaries and the cells again become oxygenated. The frequent occurrence of this paroxysmal state is the explanation of the post-mortem findings of Turner, Mott and others. The stasis is produced by a <sup>QUALITATIVE</sup> quantitative change in all the nucleo-proteid elements of the cells in epileptics, nucleo-protein forming the largest moiety of the cells of the affected layers of the cortex, of the agglutinating elements of the blood-the blood plates, and of the polymorph leucocytes whose disintegration favours agglutination and coagulation and which are found to be diminished in number after convulsions. This disintegration is the explanation of the katabolic elements found in the post-convulsive urine.

The nucleo-proteins exist in a soluble and precipitated state in the body, and the change from one to the other of these states is dependent upon a minute alteration in the reaction of their solvent or contact with a foreign body. A change of this description has been demonstrated in the fall in alkalinity prior to a convulsion and the general incidence of the convulsions in relation to the alkalinity of the blood.

The assimilation of nucleo-protein increases the element favouring coagulation in the blood. The assimilation of the components of nucleo-protein in the purin bodies and the glycerophosphates has a similar effect.

The bromides have a special affinity for nucleo-proteins and retard their metabolism.

They are present in large amounts in the polymorphonuclear leucocytes (3). They are insoluble in water except in the presence of alkali. From the alkaline solution which, if concentrated, is slightly viscous, they can be precipitated by weak acetic acid forming an amorphous white deposit. The degree of alkalinity required is extremely small and I have found in many cases the change from solution to precipitation in ten cubic centimetres of the fluid to be dependent upon the addition of one minim of 1% acetic acid. A similar proclivity to complete change of physical state by minute change in the reaction of the solvent is exhibited in resorcin, especially in freshly prepared solutions.

They are resembled by the phospho-proteins in that they contain phosphorus and have the same properties of solubility and differ in respect that the nucleo-proteins yield purin bases on cleavage while the phosphoproteins and lecithalbumins which are also allied but differ in solubility do not.

(1) Hammarsten, op. cit. pp. 90, 91, 92.

(2) Halliburton, Handbook of Physiology, 1905, p. 176.

(3) Starling, Elements of Human Physiology, p. 73.

# NUCLEOPROTEINS

While our knowledge of the chemistry of the proteins is still far from complete, sufficient is known to allow determination of many of their physical properties and the products, although not the exact chemical process, of their disintegration.

In all standard classifications the nucleoproteins are grouped as conjugated proteins along with the gluco- and chromo-proteins (1).

They are compound proteins which are characterised by yielding protein and nucleic acid on cleavage. They are present in large amount in the cells of the body: in the brain they are found in larger amount than any other protein(2) and are particularly abundant in the polymorphonuclear leucocytes(3). They are insoluble in water except in the presence of alkali. From the alkaline solution which, if concentrated, is slightly viscous, they can be precipitated by weak acetic acid forming an amorphous white deposit. The degree of alkalinity required is extremely small and I have found in many cases the change from solution to precipitation in ten cubic centimetres of the fluid to be dependent upon the addition of one minim of 1% acetic acid. A similar proclivity to complete change of physical state by minute change in the reaction of the solvent is exhibited in resolution, especially in freshly prepared solutions.

They are resembled by the phospho-proteins in that they contain phosphorus and have the same properties of solubility but differ in respect that the nucleoproteins yield purin bases on cleavage while the phosphoproteins and lecithalbumins(which are also allied but differ in solubility) do not.

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(1) Hammarsten, op. cit. pp. 90, 91, 92.

(2) Halliburton, Handbook of Physiology, 1905, p. 176.

(3) Starling, Elements of Human Physiology, p. 73.



The mucins exhibit a similar solubility but contain no phosphorus. In the nucleoproteins the phosphorus is contained in what Kossel calls the 'prosthetic' group or side chain(1), consisting of nucleic acid which can be split off from the protein whereas in the phosphoprotein a simple salt-like formation obtains between the phosphorus-containing moiety and the protein.

The brain also contains a large number of other phosphorus-containing substances of the cerebroside class and protagon which is considered by Cramer to be an integral substance; also the ether-soluble lipoids of which the chief is Lecithin, which also contain phosphorus.

The variations and interactions of these substances are extremely rapid and complicated and can only partially be reproduced in vitro.

As the nucleoproteins occur in the cells, they are in most cases soluble in water or salt solution which is comparable to the lymph, but after separation they need the presence of a small quantity of free alkali for their solution(2). When freshly prepared from protoplasm they are highly unstable and undergo changes in p repeated precipitations and resolutions.

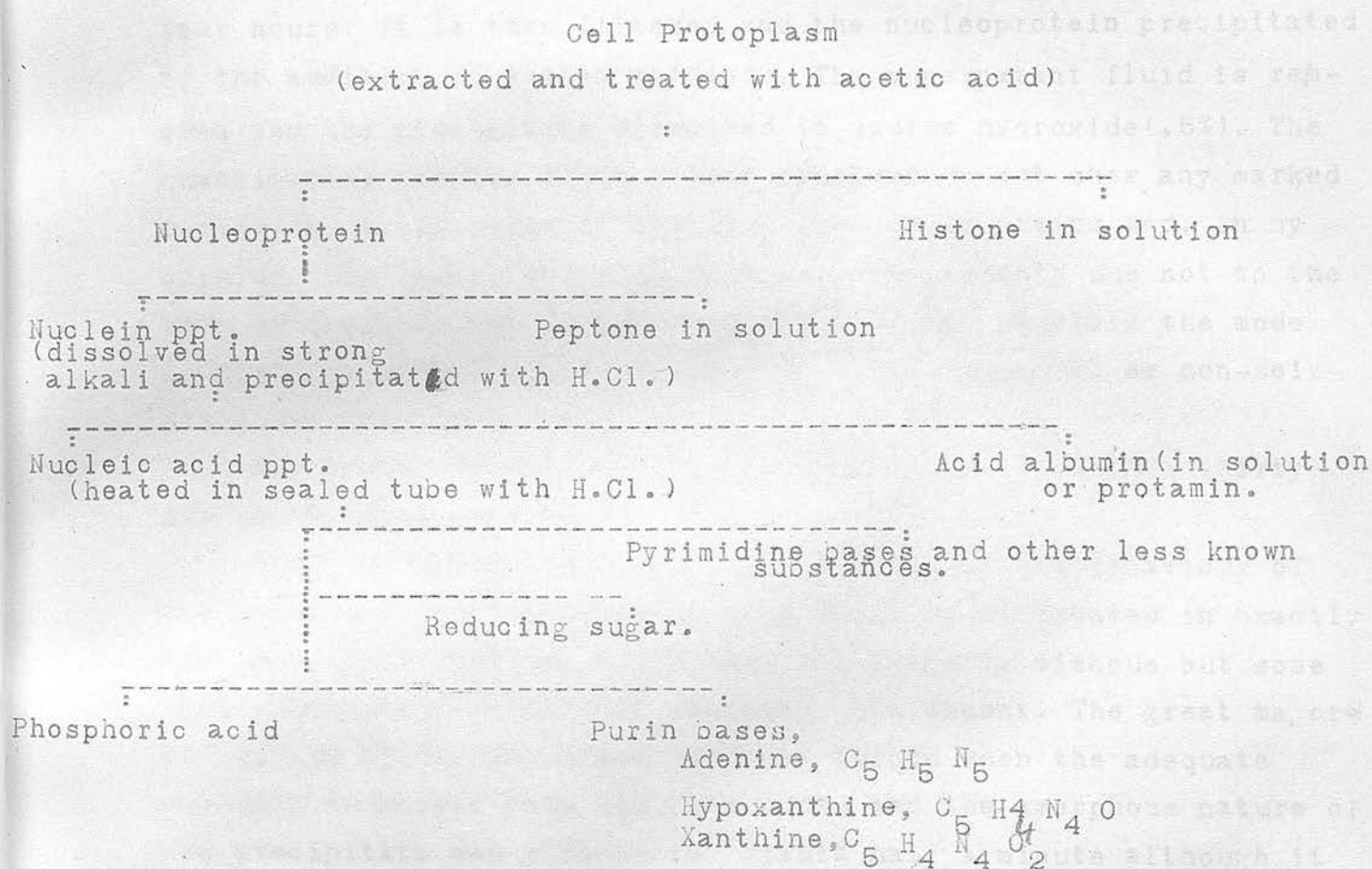
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- (1) Hammarsten, op. cit. p.171.
- (2) Starling, Elements of Human Physiology, 8th Ed. p.43.

A solution of nucleoprotein can be obtained from many of the tissues and in considerable quantity from the brain. In appendix I are stated the results of a series of quantitative estimations of

(1) Starling, op. cit., p. 43.

(2) Starling, op. cit., p. 447.

The disintegration of nucleoprotein may be carried out in vitro as follows(1)--



Uric acid ( $C_5H_4N_4O_3$ ) is also a purin although its exact relation to the other bases and to cellular metabolism has not yet been fully demonstrated. It is probable that part of the basic residue of nucleoproteins may undergo oxidation in the body and appear in the urine as uric acid while another part may escape oxidation and appear as the so-called alloxuric bases.(2)

A solution of nucleoprotein can be obtained from many of the tissues and in considerable quantity from the brain. In Appendix I are stated the results of a series of quantitative estimations of

(1) Starling, op. cit., p. 44.

(2) Starling, ibid., p. 447.

nucleoproteids and ether-soluble substances in brains from various forms of insanity. The brain substance is finely macerated and placed in an aqueous solution of Sodium Carbonate (1.5%) for twenty four hours. It is then filtered and the nucleoprotein precipitated by the addition of acetic acid (1%). The supernatant fluid is removed and the precipitate dissolved in sodium hydroxide (.5%). The quantitative results which I have obtained do not shew any marked variation in the cases of epilepsy from other brains and, in my opinion, the quantitative differences are probably due not to the form of insanity but to personal differences: possibly the mode of death in different cases, slow or rapid, seizural or non-seizural, may have some influence.

All brains were placed in the first solution within thirty six hours after death.

There were wide individual differences in the behaviour of the solutions in precipitation and resolution. Treated in exactly the same manner the solutions were all slightly viscous but some were translucent and others markedly opalescent. The great majority of the solutions became suddenly turbid when the adequate quantity of acetic acid had been added and the amorphous nature of the precipitate was observable within half a minute although it settled slowly in the long graduated tubes which I used. In other cases although the opacity increased suddenly the aggregation of the particles to form the amorphous precipitate did not occur until an hour after the acid had been added.

In one case from an imbecile brain while the opacity was increased by the addition of acetic acid, no precipitate appeared in twenty four hours but I then obtained a small precipitate containing a minute trace of phosphorus by adding fifteen minims of 10% nitric acid to the thirty c.c.s of solution. I estimated the phosphorus contents in the thirty seven samples of nucleoproteid and thirty one of the lipoids and found that it bore a fairly constant ratio to the amount of the precipitate.



In two samples which were prepared with half the usual amount of sodium carbonate solution to the same quantity of brain substance, I obtained, by carefully adding the weak acid to the alkali solution in a series of test tubes, a precipitate when the reaction was neutral to the sensitive litmus of Kubel and Tieman, but in five other similar concentrated solutions no precipitate appeared until the solution turned acid.

The precipitated nucleoproteid has a ready affinity for basic dyes. In two specimens which I allowed to stand for over a week in the precipitated state, I found when examined microscopically a few well marked crystalline rosettes exactly resembling the crystals of Uracil, a pyrimidine body, among the debris; the majority of stale precipitates shewed no such change.

I found that the addition of various salts produced a similar phosphorus-containing precipitate to that of acetic acid, those most rapid in effect being calcium and sodium chloride and magnesium sulphate. The addition of saturated calcium chloride to a quantity of macerated brain produced a thick coagulum which lay at the top of the solution. In some cases this reaction was so rapid that, using test tubes of an inch diameter, the whole tube could be inverted without the fluid flowing past the coagulum, within half an hour. No other salt produced such a rapid effect as calcium in this way. This effect could not be produced upon the residue left after the nucleoproteid extraction by sodium carbonate and I surmise that calcium, which is always found in brain substance, has a special coagulative effect in strong solution upon the unaltered nucleoproteid elements, although it produced a simple precipitate and not a coagulum from the alkaline solutions.

In addition to the nucleoproteid elements of the cells of the brain the following substances can be found- the purin bases, paralactic acid, phosphocarnic acid and uric acid(1). Metabolism is always most rapid and complete when the fluid which bathes the cells is alkaline. The process of metabolism causes the accumul-

ation gradually diminishes the degree of, or prevents further change and so the equilibrium of the metabolism of the cortex like the rest of the body is maintained. I have already referred to the extreme fineness of the cortical capillaries and to the comparatively large perivascular lymph spaces by which the interchange between blood and tissue cells is rapidly effected.

#### The Action Of The Halogens Upon Proteins.

The relation between Chlorine, Bromine and Iodine and the proteins has only recently received any considerable degree of attention although as long ago as 1848 Mulder obtained a precipitate which he called 'protein chlorous acid' when chlorine was passed into a solution of egg albumin. The method which is now chiefly used(1) is the passage of a stream of chlorine or bromine through a weakly alkaline solution of protein. Blum and Vaubel found that it was only in an alkaline solution that the maximum halogen-protein combination could be obtained. "A definite series of bromine derivatives was obtained from proteids each with a constant amount of bromine by varying the methods of preparation. It was not found possible to obtain such a definite series with either the chlorine or iodine preparations".

The precipitate formed is soluble in 1% sodium hydroxide and suddenly reprecipitated by addition of a slight excess of weak acetic acid.

It is interesting to observe the exact similarity in the solubility of these compounds and that of the nucleoproteins, especially in view of the fact that both the substances used in these investigations-caseinogen and ovalbumin, contain phosphorus in protein combination in considerable quantity.

(1) S.B.Schryver, Ph.D., D.Sc. The General Characters of the Proteins, 1909, pp. 61-67.

From my own observations, I believe that the halogen affinity is greater in the case of the phosphorus-containing proteins and especially the nucleoproteins than in any other group.

I have observed the effect of bromination upon a considerable number of solutions of nucleoprotein obtained from brain and find that in bulk and weight the bromine precipitate was usually ~~st~~ slightly larger than that obtained by precipitation by acetic acid. The bromine solution was prepared by slightly heating manganese dioxide and pure hydrochloric acid in a strong flask with a curved outlet tube from the neck. The stream of chlorine was led to the bottom of another flask, also slightly heated, in which lay a saturated solution of potassium bromide. I placed the solution to be brominated in an ordinary Soxhlet fat extraction tube, allowing the bromine to enter by the thin looped tube at the bottom so that it bubbled up through the contained fluid. By this means the sudden precipitation of the halogen compound is well demonstrated. By variations in the degree of heat applied to the two flasks the supply of bromine, as shewn by the rate of bubbling into the Soxhlet tube, could be maintained uniformly. The time taken for precipitation varied from three quarters of a minute to seven minutes with no obvious cause except individual differences in the stability of the nucleoproteins and their bromine affinity. A similar but less satisfactory result was obtained by quickly passing a few drops of bromine in liquid form to the bottom of a large Stokes tube containing the solution and then agitating the tube.

Examination of solutions which have been subjected to bromination, but not to the degree of precipitation, shewed the important fact that a slightly larger amount of acetic acid is required to effect precipitation of the nucleoprotein than in a simple solution through which no current has been passed. Bromine precipitate likewise requires the addition of slightly more alkali for solution than the simple precipitate. This difficulty in precipit-



ation and resolution increases as time elapses, and I have found that a bromine precipitate kept for two months in a stoppered tube is very slowly soluble even in 5% sodium hydroxide. This also applies in a less degree to the non-brominated precipitates.

In addition to the alkaline solution, the blood plasma and cerebro-spinal fluids exhibit a similar sudden precipitate on bromination but, owing possibly to the small quantities available, I was only able to be sure of the presence of phosphorus in two samples of blood plasma out of four and in none of the cerebro-spinal fluids of which I tried five.

Phosphorus was present in all the bromine precipitates of nucleoprotein from brain. It is probable that the action of the bromine is to precipitate the nuclein and a varying protein moiety. Whether this is due to the substitution of hydrogen by bromine is not known. From the behaviour of the precipitate in the partially brominated solution, I have come to the conclusion that the effect of the halogen union is to fixate the large nucleoprotein molecule and render it less liable to rapid change. If this be so the presence of bromine in the nucleoprotein of the living cells would act as a restraining influence upon its metabolism.

This view was formed chiefly upon the foregoing observations of increased resistance to change of physical state. The action of the bromide salts upon the albuminous bodies of a sensitised photographic plate in restraining the rapid chemical changes therein on exposure and development is interesting.

Albertoni(1) has observed that a considerably stronger current of electricity is required to excite the cortical motor neurons of a dog which has been dosed with bromide. The iodine content of the iodothyreoglobulin has been shewn to be high after potassium

(1) Sarnyver, op. cit. p. 26.

(2) W. Albertoni, *Nature*, vol. 125, p. 231, 1905, quoted by Aldren Turnel.

(1) (Albertoni) Aldren Turnel, *Epilepsy*, p. 231.

5. *Small Diagnostic Methods*, p. 781.

iodide administration(1), and Falta states that "iodised albumens are metabolised more slowly than simple albumens"(2).

In addition to the glycogen reaction of the blood which is found in certain serious conditions, an intracellular and extracellular reaction has been shewn to be present in physiological conditions(3). By the action of iodine vapour on moist smears, a granular staining of the protoplasm of the lymphocytes and a diffuse staining of the polymorphs have been exhibited. A similar extracellular iodine reaction has also been found which Cabritschewski and Zollikofer have shewn to be masses of blood plates. This extracellular reaction is also found at times in healthy blood and in states of acidosis such as diabetes, the cause of its variability in healthy blood not being known. I examined a number of epileptic bloods by this means and was surprised to find the reaction present in six out of the first eight cases which I tried. I substituted bromine for iodine vapour and was impressed by the appearance of a marked reaction in my own blood, distinct extracellular granules being visible and the nuclei, especially those of the polymorph cells, being very well defined. I am convinced that the extracellular elements consisted of blood plates and I believe that the variations in the stainability of the intracellular granules is exactly comparable to the changes in the affinity for the basic dyes observed by Gage and Mann which will be described in a later paragraph. If my assumption that the stainability is dependent upon the nucleoproteid content of the blood be correct, its greater definition in the hypo-alkaline or slightly acid states such as uraemia and diabetes is explainable. I obtained well marked positive results, by a variation of the method, in every epileptic case which I examined. A strong aqueous solution

(1) Schryver, op. cit. p.38.

(2) W.Falta, Naturf Ges zu Basel XV, No.2, 1903, quoted by Mann, Chemistry of the Proteids, 1906, p.233.

(3) Sahli Diagnostic Methods, p.781.

of bromine water was prepared and a drop of this was mixed with an equal sized drop of blood upon a cover slip and at once mounted in levulose on a slide. Stained in this way the nuclei of the leucocytes are exceedingly well defined and the blood plates can easily be counted in relation to the leucocytes, the red cells being to a large extent haemolysed. These blood plate enumerations vary, however, so greatly in slides prepared from the same case at the same time that no statement as to their number would be of the slightest use, and I believe that their variation was not due to the staining method but to the great rapidity with <sup>which</sup> the blood plates change in number in shed blood in process of extrusion from or disruption of the polymorph cells and in their speedy disappearance as entities as they interact with prothrombin to form thrombin. The widely different results which all observers have obtained in blood plate enumerations contrasted to the counts of the real formed elements, the white and red corpuscles, support this view and any comparative ~~method~~ estimation made by any method is liable to be fallacious unless the fixation of the plates can be effected at precisely the same second from the time at which the blood leaves the blood channels.

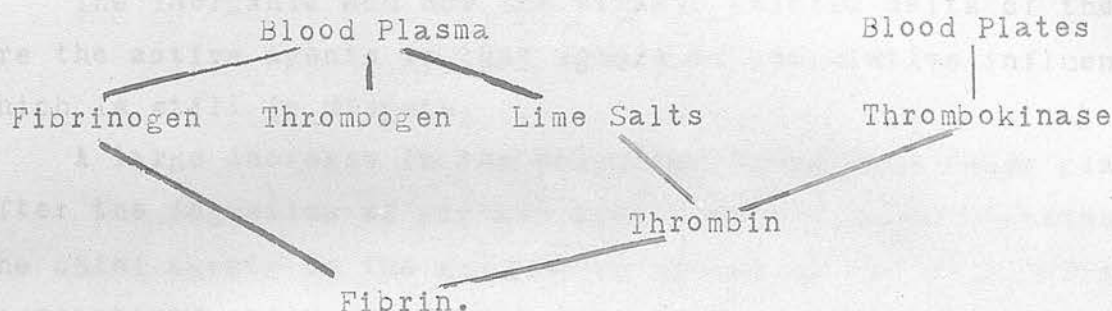
In the blood as in the brain the nucleoproteid content is high and is of great importance in the production of agglutination and coagulation. The viscosity and coagulability of the blood can be altered by dietetic and medicinal means by the increased ingestion of nucleoproteid and its components.

The disruption of the polymorph cells increases the purin content of the blood and so the secretion of uric acid. We have seen that the sudden introduction of nucleoproteid in excess into the blood of animals is productive of extensive intra-vascular coagulation, of epileptiform seizures and with sufficient amount, death. We also know from the observations of Turner that the nucleoproteid coagulative elements are found in excess in the cortical blood vessels of epileptics and, from the observations of Mott,



that a biochemical change occurs in the cortical cells rich in nucleoprotein, dependent upon the condition of the surrounding lymph.

The theory of fibrin formation in most general acceptance may be illustrated thus:-(1)



The constitution of these substances, so far as is known, is as follows:-

Blood Plates(Nuclein plates of Lillienfield) are a nuclein protein combination(2),containing a large phosphorus quotient. They are generally considered as derivatives of the white cell nuclei, especially those of polymorph(3). They consist of,or contain in large amount, thrombokinese which is found in the white cells and tissue cells rich in nucleoprotein(4).

Prothrombin is also a nucleoprotein according to the researches of Pekelharing; Huiskamp has shewn that it occurs in the thymus as a nucleo-histone and also in another form(5)

(1) Starling, Human Physiology,p. 82.

(2) Hammarsten, op. cit.,p.296p

(3) Gulland and Goodall, op. cit.,p.71.

(4) Gulland and Goodall, ibid.,p.217.

(5) Hammarsten, ibid.,p. 248.

Thrombin which is the resultant of the interaction of pro-thrombin and thrombokinase, is also a nucleoprotein(1).

Fibrinogen is a globulin or possibly a compound fibro-globulin, the fibrin being precipitated and the globulin going into solution.

The inorganic and not the organic calcium salts of the blood are the active agents in that sphere of coagulative influence which is still in dispute.

A large increase in the polymorph leucocytes takes place after the ingestion of protein rich bodies(2). The proteins are the chief agents in the production of the so called digestion leucocytosis, being more effective in this way than the fats. Gage and Mann(3) have also shewn a large increase in the nucleoprotein elements of the blood and an increase in their stainability after the ingestion of protein substances and of the phosphorus rich substance Sanatogen.

It has been shewn that the injection of nucleinic acid constantly causes a hyperleucocytosis without increase in the mononuclear cells(4). The assimilation of nuclein rich foods causes an increase in the output of the purin bases and uric acid in the urine. Purin bases when assimilated also increase the uric acid excretion; this in part is due to a direct alteration in the purin bodies and the blood and partly to a disintegration of the nucleoprotein of the cells(5). In leucocythaemia, in which there is an

(1) Hammarsten, op. cit. p. 250.

(2) Gulland and Goodall, ibid., p. 63.

(3) Gage and Mann, "Changes in Blood by Feeding" Lancet, Oct. 19th, 1912.

(4) E. Merk, Annual Report, 1911, p. 329.

(5) Hammarsten, op. cit. pp. 666, 667.

(6) Halliburton and Brodie, Journal of Physiology, Vol. 17.

(7) Prof. Henry Meyer, S.M.J. 11/10/1894.

excessive leucocyte formation and destruction, the purin bases of the blood and urine are markedly increased(1). Albumosuria is common and a diminished alkalinity of the blood is stated to be present(2).

We know that a great destruction of the leucocytes takes place on coagulation and this is most marked in the polymorphs.

The relation between diminished alkalinity of the blood and increase in the viscosity and coagulability has also been mentioned. That the blood in epilepsy at all times and especially immediately prior to a fit is hypo-alkaline has been demonstrated, and also the relative decrease in the polymorph cells after a convulsion(3).

Lowit has observed that agents which, when injected intravenously, cause a leucocytosis, produce as an immediate primary result a leucolysis; among such substances are peptone, nuclein and uric acid(3).

These facts, together with the evidence in the urine of nucleoprotein decomposition in the uric acid, phosphates and albumosuria, are strong indication that such a change in the leucocytes occurs at the convulsive period with its attendant coagulative effect. The presence of nucleoprotein coagulants in the cerebral blood vessels strengthens this opinion.

A considerable reduction in the alkalinity of the blood in the acid states such as diabetes, uraemia and eclampsia, in all of which convulsions occur, has a further effect. In all acid intoxications the calcium content of the blood increases, apparently at the cost of the tissues(4). Very slight alterations in the percentage of calcium causes a profound change in the nucleoprotein

(1) Hammarsten, op. cit. pp. 183, 676.

(2) Lazarus-Barlow, op. cit., p. 148.

(3) Halliburton and Brodie, Journal of Physiology, Vol. 17.

(4) Prof. Henry Meyer, B.M.J. 11/10/1894.



substances(1). I consider it highly probable that in the increasing acidity of the blood in status epilepticus the calcium content of the blood increases in this way and so develops the stasis and agglutination which produce the ordinary fit into a coagulation with fibrin formation which leads in most cases to death.

We have seen the effect of the mass action of Carbon Dioxide, suddenly applied, in increasing the alkalinity of the serum. I believe that this change tends to prevent further leucolysis when the convulsion has once taken place. Along with the increased pulse rate, the rise in blood pressure and the aid of anastomotic channels, the sudden cyanosis thus acts as a remedial agent in a convulsion.

#### The Exciting Cause of a Convulsion.

The application of the preceding sections upon the metabolic changes of nucleoprotein in brain and blood to the convulsive manifestation, will form the conclusion of this thesis.

The acid products of metabolism- in the body chiefly lactic and carbonic acid, and in the nucleoprotein rich cells such as the cortex, uric and carbonic acids- these products tend to inhibit further metabolism. Additional factors also arise. The increase of viscosity of the blood in the capillaries causes a slight slowing of the stream and a diminished supply of oxygen. The diminution of metabolism is further reflected upon the rate of flow, the metabolic activity of the cells being, per se, an influence in stimulating capillary circulation in the cortex by the rapid movement of the protein atoms and molecules in and between the cells, lymph spaces and fine capillary channels(2).

The result of prolonged mental exertion produces physiological indicants to rest in drowsiness, impaired perception and dulling of the special senses along with impaired motor control. If

(1) Mann, Chemistry of the proteids, p. 456.

(2) James Capple, M.B. Brain, 1898, p. 58.

the required rest be not afforded these symptoms develop into headache, irritability and in advanced fatigue a tendency to insomnia owing to the morbid stimulation of the cells by the toxic accumulants. If however rest be taken in the earlier stages of fatigue, sleep ensues. To effect this state of rest the stimulation of the special senses is diminished by darkness and silence. The adoption of the recumbent position causes congestion of the cerebral vessels. These vessels dilate and this, in the cortical regions, causes the entrance of the lymph with its acid contents into the blood stream and further increases viscosity. The slackening of the stream is furthered by the lessened force of the heart's action, by a slight fall in the blood pressure and by the diminished effect of the respiratory pump as respiration becomes slow and shallow. The application of warmth also favours agglutinative change. The result of the interaction of all these factors is a gradual "sleepening" and ultimately sound sleep when the metabolism in the cortical areas is at a standstill. The reflex ponto-medullary centres which controll the vital functions are not similarly affected because of the differences, already mentioned, in the calibre of the capillaries and the completely different lymph vascular arrangement which exists in all regions outside the cortex.

As the viscosity and sluggishness of the cortical capillary stream increases the sleep deepens and it has been demonstrated experimentally (vide page 17) that viscosity is greatest at the time of deepest sleep.

The acid accumulants are gradually removed from the blood by the kidneys and skin and the capacity for action of all the cells of body and brain is slowly but completely restored. As the alkalinity increases the proclivity to rapid metabolism reappears and slighter and slighter stimuli will provoke excitation of the cortical cells and a return to consciousness.

In relation to these phenomena which are gradual and self-regulative in their action there are numerous deviations in the healthy subject which are relevant and important.

After excessive exertion, especially mental, a familiar occurrence is the sudden start which rouses an incipient sleeper. "It is an insubordinate action of the motor centres occurring during the gradual withdrawal of the higher control"(1). It is due in my opinion to a degree of stasis produced by the entrance of the acid katabolic substances to the blood stream from the large lymph spaces in the motor areas, so suddenly effected that a sudden failure in the oxygen supply is produced instead of a gradual diminution.

Sudden night terrors and the phenomena of somnambulism are due, I believe, in a large measure to an absence of harmony in the progression of the various factors which produce and maintain unconsciousness.

If the cardiac action be irregular, agglutination may occur on a sudden fall in the pulse rate when the highly viscous blood is slowly passing through the capillaries and a sudden increase in the carbon dioxide in the lymph takes place: a morbid toxic stimulation of the cells occurs and the phenomenon of the Stokes Adams seizure is evinced.

If, on the other hand, an ordinary syncopal attack occurs by day the blood pressure falls more slowly and the blood not being in an especially agglutinative state, unconsciousness is produced with less rapidity.

(1) Sir William Cowers, "The Borderland of Epilepsy", 1907, p. 107.



If the defective factor be the blood and lymph contents, a state of narcolepsy may be similarly produced at any hour of the day but more commonly after meals by a comparatively slow induction of morbid cortical stasis.

These conditions form the connecting link between the one extreme of healthy physiological conditions of cortical activation and inactivation- of waking and sleeping, and the other extreme of the epileptic state in which the blood and lymph aberrations produce the morbid excitant effects of stasis instead of gradual unconsciousness.

In the epileptic, metabolism is at all times carried on in the minimal degree of alkalinity of the blood and lymph. The equilibrium of the cerebral circulation, delicate in the healthy, is reduced to an extreme degree of instability in epilepsy. Any excitant or further increase in viscosity, stasis and agglutination may provoke a convulsion. Therefore we find that the attacks occur at the times when there is a slight natural tendency to stasis- at the inception of sleep, in the hours of deep sleep and when the coagulative elements of the blood are high after the ingestion of nucleoprotein and purin.

The decrease in the polynuclear cells which are coagulative elements and the appearance in the urine of the decomposition products of coagulative bodies serve to indicate that agglutination must have occurred. The discovery of evidence of such agglutination in excess in the epileptic brain supports this statement. The effect of the administration of alkalis in raising the blood state from the danger level of marked hypo-alkalinity; of the bromides in fixating the cortical acid producing substances and the coagulative elements of the blood; of digitalis in raising the general level of blood pressure- these lend support from the therapeutic standpoint to this view.

I believe that the epileptic phenomena are due to a morbid development of one factor in the natural physiological regime- the reduction of alkalinity dependent on metabolism and the effect of the comparative acidulation of the serum upon the coagulative elements of the blood; also that this acidulation of the lymph and blood is produced by too rapid metabolism of the nucleoproteid content of the cortical cells and other nucleoproteins which, in the circulating media, shew a proclivity to abnormally rapid agglutination. The primary cause is thus an inherent defect in the nucleoproteid tissue elements which may be hereditary.

state of the blood exist in epilepsy which render such a state possible at any moment.

Such a sudden agglutination may be produced when the nucleoproteid elements of the blood are increased by ingestion of nucleoproteid purine and at the inception of sleep and too advancing stage of its profundity.

The post-epileptic changes in the blood and urine indicate that a rapid disintegration in the nucleoproteid elements has occurred.

The post-epileptic findings indicate the excessive production in the cells of such nucleoproteid agglutinations in the cortical cells and an excessive biochemical change in the cortical cells which are rich in nucleoprotein.

The administration of alkalis reduces the coagulative tendency of the blood and reduces the number of the convulsive attacks other than temporary. The alkalis have a particular affinity for the nucleoproteins and act as inhibitors of their rapid metabolism. This diminishes the acidulation of

## GENERAL SUMMARY.

The manifestations of epilepsy- the convulsive seizure and the minor attack- are due to a sudden anaemia of the cortex causing a discharge of the cortical nerve cells.

This anaemia is produced by a sudden stasis and agglutination of the nucleoproteid coagulative elements of the blood in the cortical capillaries.

An unusual proclivity to agglutination and a hypo-alkaline state of the blood exist in epilepsy which render such a stasis possible at any moment.

Such a sudden agglutination may be produced when the nucleoproteid elements of the blood are increased by ingestion of nucleoprotein and purins and at the inception of sleep and the advancing stages of its profundity.

The post-paroxysmal changes in the blood and urine indicate that a rapid disintegration in the nucleoproteid elements has occurred.

The post mortem findings indicate the excessive production in the brain of such nucleoproteid agglutinations in the cortical capillaries and an excessive biochemical change in the cortical cells which are rich in nucleoprotein.

The administration of alkalies reduces the coagulative tendency, but, by facilitating metabolism, cannot reduce the number of the convulsive attacks other than temporarily. The bromides have a particular affinity for the nucleoproteins and act by inhibiting their rapid metabolism. This diminishes the acidulation by



uric acid of the contents of the cortical perivascular lymphatics and capillaries and also renders the polymorphonuclear cells and the other nucleoproteid coagulative elements of the blood less liable to sudden change. The oxalates act by inhibiting agglutination.

The essential defect is the chemical instability of the nucleoproteid elements of the brain and blood which may be hereditary or due to the absence of a regulating hormone at present unknown.

E. Urine Estimation

(p. 22)

F. Renal Excretion Charts

(p. 23)

G. Summary of Treatment

(p. 24)

H. Observations on Vaso-motor Variations

(p. 25)

I. Tables of Nucleoprotein and Lecithin content in Brain (p. 26)

### Bibliography.

For the privilege of using the clinical material recorded in this thesis I am deeply indebted to Dr Stansfield, Medical Superintendent, and to the Huxley Sub-Committee of the L.C.G. Asylums Committee.

## APPENDICES.

- Description by an epileptic patient of a "protracted warning" and the incidence of his convulsions at the onset of sleep.
- A. Description by an epileptic patient of a "protracted warning" (p. 8)
  - B. Heredity Tables (p. 10k)
  - C. Blood Agglutination and Calcium Content (p. 19k)
  - D. Leucocyte Counts (p. 21)
  - E. Urine Estimation (p. 23)
  - F. Phosphate Excretion Charts (p. 23)
  - G. Summary of Treatment (p. 25)
  - H. Observations on Vaso-motor Variations (p. 30)
  - I. Tables of Nucleoprotein and Lecithin content in Brain (p.35)

## Bibliography.

For the privilege of using the clinical material embodied in this thesis I am deeply indebted to Dr Stansfield, Medical Superintendent, and to the Bexley Sub-Committee of the L.C.C. Asylums Committee.

Dr Shaw.

Description by an epileptic patient of a protracted warning and the incidence of his convulsions at the onset of sleep.

This patient is sufficiently sensible and well behaved to be in one of the two male wards in this institution which are staffed by female nurses.



Dr Shaw,

Sir,

A few days before I have a fit I generally have a slight pain in my head at the top and I think to myself there is one not far off. A couple of days or more may go by and then when I go to bed I cannot go to sleep so I then know what is coming. I lay still and try to sleep and as soon as I close my eyes and try to drop off I suddenly see a small light like a little star dancing in my eye. I sit up in bed and grasp my left wrist tight with my right hand pressing the artery. I call the nurse and ask her to stop a minute. Then wherever I look things seem to be moving and the star in my eye seems to get stronger and flicker more, and then when I begin to think I am going off it will stop all of a sudden and I feel quite relieved. I let go my wrist and perhaps I am right for a week or two. I struggled with one about two years ago. It started on my arm but I hung on and it stopped all of a sudden and left my arm moving about all on its own accord for a time. I suppose it was the nerves but I did not have another fit for close on five months.

Your obedient servant,

James A. Chater.

G. L.  
Appendix B.

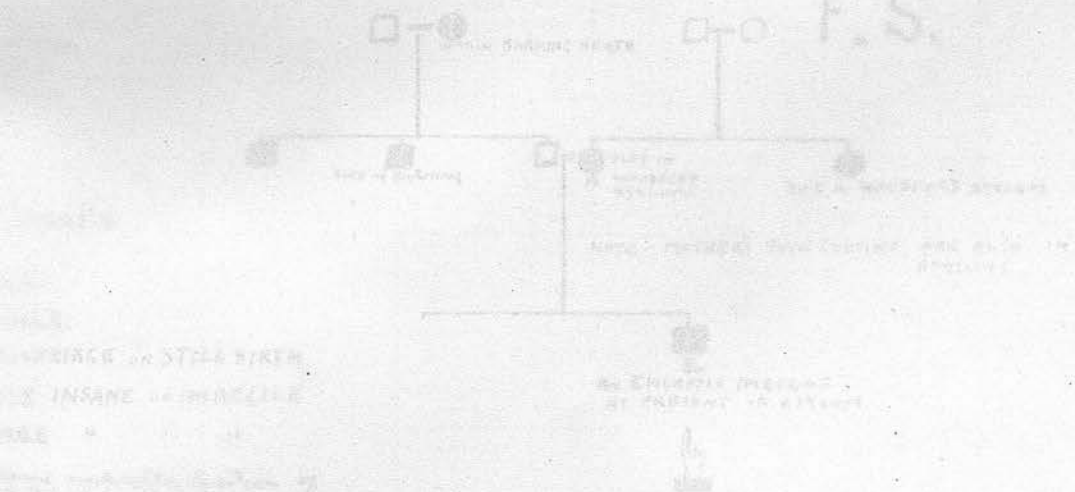
Heredity Tables of three Epileptic patients with epileptic and insane heredity, and of three Non-epileptic cases with epileptic heredity.



S. D.

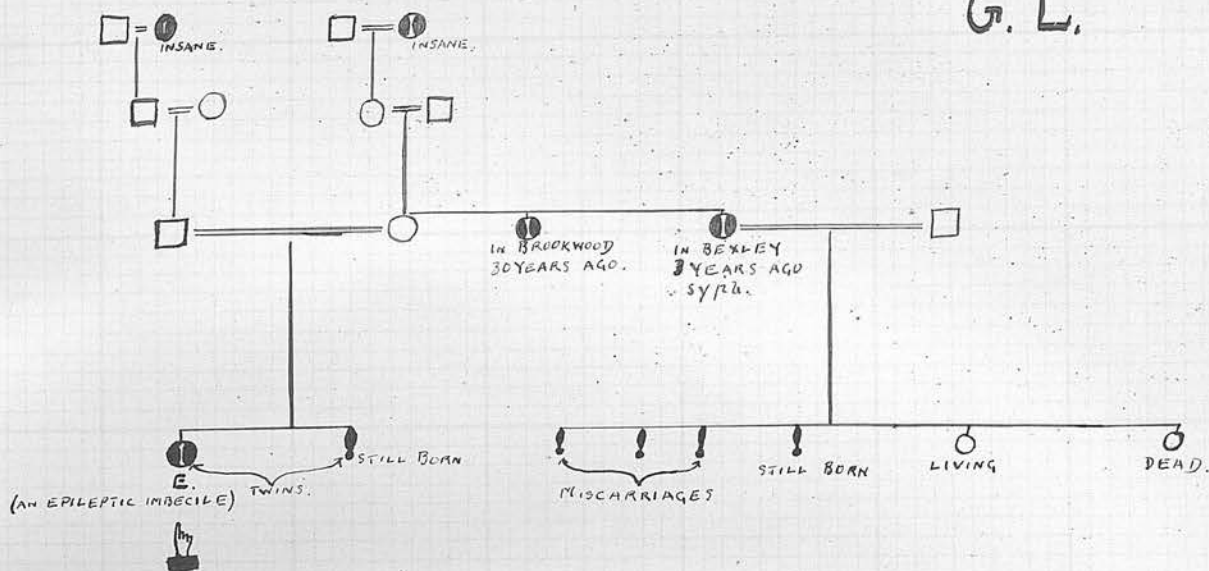


F. S.

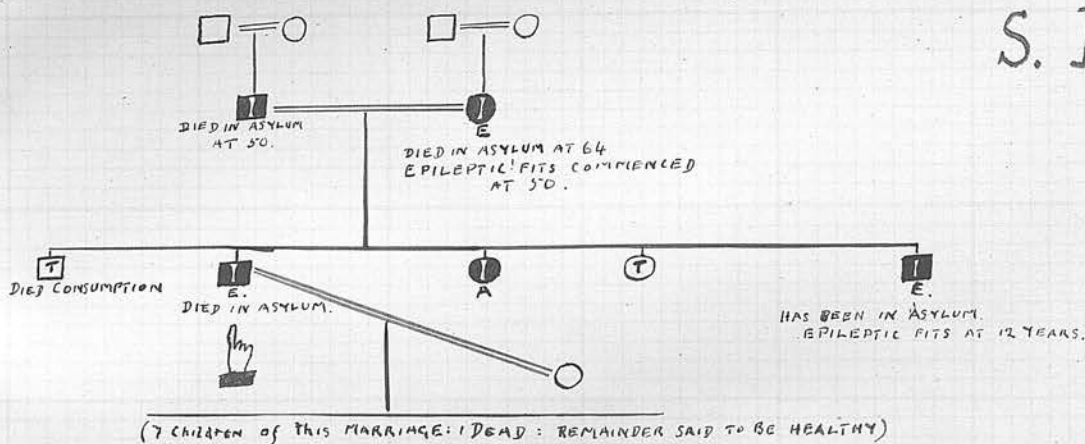


Legend:  
E - Epileptic  
I - Insane  
T - Consumption

G. L.

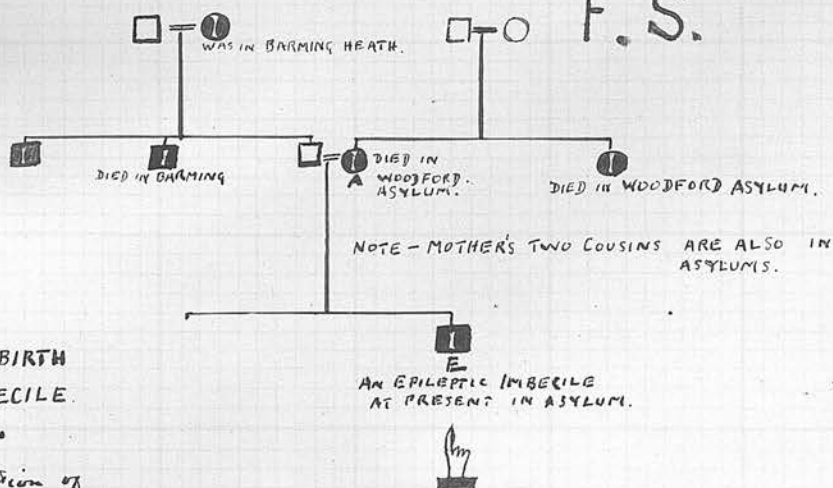


S. D.



(7 CHILDREN OF THIS MARRIAGE: 1 DEAD: REMAINDER SAID TO BE HEALTHY)

F. S.



## KEY TO CHARTS

- = MALE.
- = FEMALE.
- ! = MISCARRIAGE OR STILL BIRTH
- = MALE INSANE OR IMBECILE.
- = FEMALE " " "

The Hand indicates Position of Patient in Sequence.

THE LETTERS.

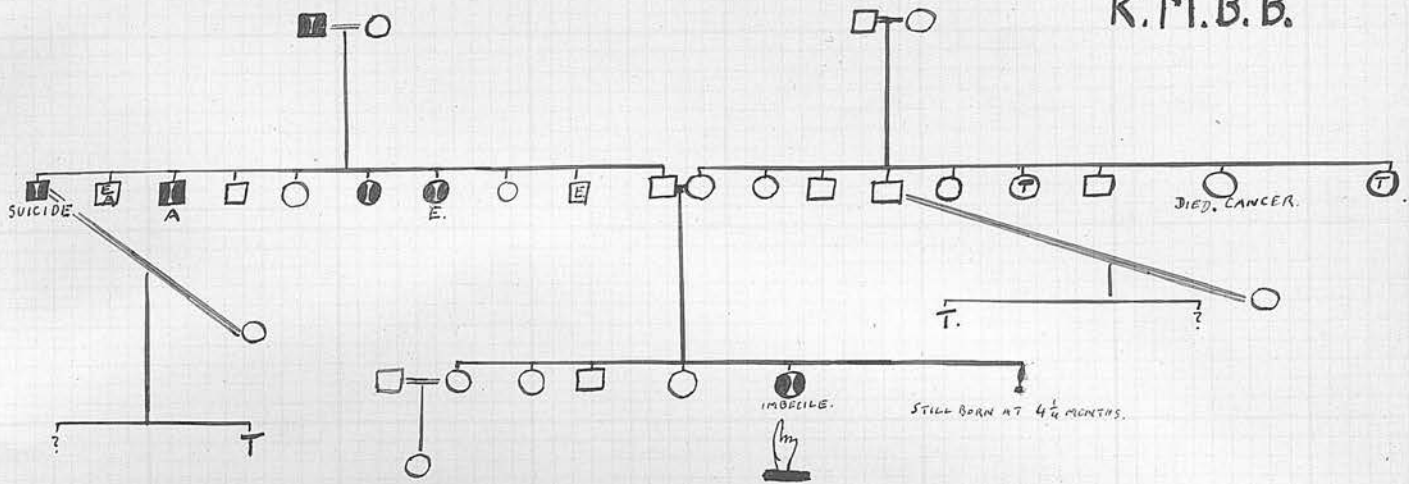
E = Epileptic.

A = Alcoholic

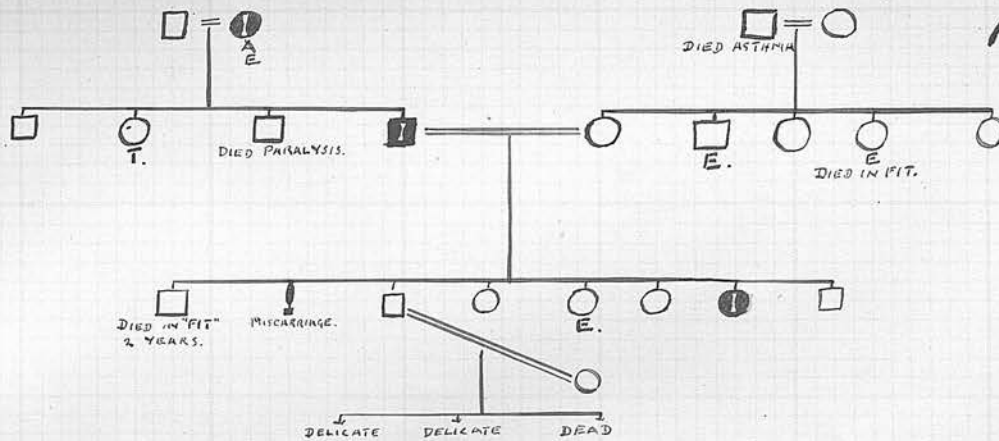
T = Consumptive



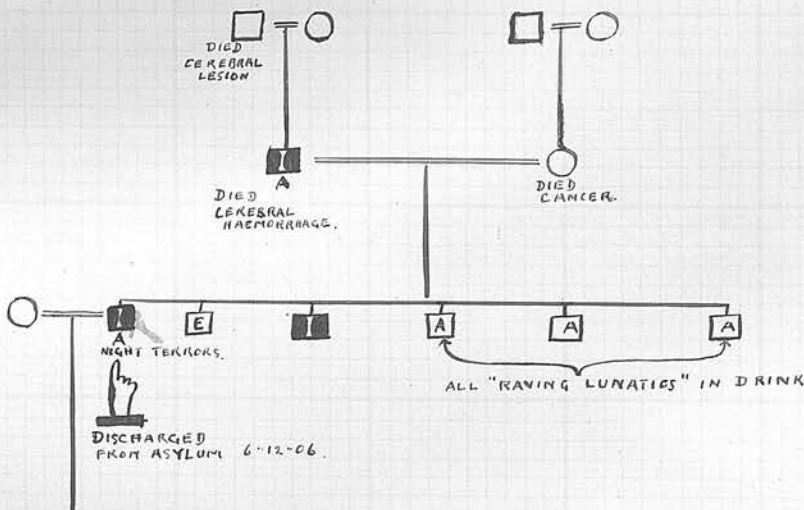
K.M.B.B.



A.M.B.



W.A.



7 CHILDREN. - 3 DEAD - OTHERS UNKNOWN.

The essentials of Wright's method of estimating the calcium content of the blood have been described (p. 18).

From observation of the blood of epileptics, I am convinced that the agglutinative action is one of unusual rapidity.

Working with all possible speed and drawing the drops as soon as intermixed into the long tube I managed to obtain a fairly large number of samples. But using the method recommended by Wright, which is quite simple in non-epileptic blood, of making the series of intermixtures on the slide and then proceeding to draw them one by one into the long tube for observation, I never improved upon the percentage of agglutinations which impressed me upon the first trial of epileptic blood in which only five out of a total of thirty-two intermixtures could be drawn into the tube.

As I soon became aware that the results from the point of view of the calcium content would be worthless, I used only three of Wright's dilutions ( $N/80$ ,  $N/180$ ,  $N/320$ ) of ammonium oxalate in physiological saline and supplemented them by two strong solutions of sodium chloride and one drop of unmixed blood.

I regret now that I did not attempt to estimate the calcium by Blair Bell's calcimeter after trying Wright's method, but had I done so at first (in Bell's method the blood is drawn straight from the drop at the site of puncture with no exposure on a slide) I might not have observed the rapid agglutination to which great importance is to be attached. To determine the presence of clot, unless its distinct formation could be seen in the capillary tube, I expressed them into water. Before estimating the results the tubes were kept for twelve hours in a Hearson incubator at  $37^{\circ}C$ ,

# EPILEPTIC (continued)

Eight samples of ammonium oxalate dilution of blood.

J.H.C. (m) Two only obtained (N/240 and N/280). Neither clotted in

NON-EPILEPTIC:-ce. On expression into water the small amorphous masses dispersed at once.

W.D.(m), Calcium Content N/80 no clot - 0.58 parts of Ca O in 1000

A.W. (m) Three weaker N/100 one only obtained, no clot in tube.

W.M. (m) : : N/120 no clot- 0.41 : : :  
N/150 clot

J.J.M.S. (m) : : N/200 no clot - 0.26 : : :  
N/240 clot

S.A.B. (m) : : N/100 no clot - 0.5 : : :  
N/120 clot

In this case dilution N/280 agglutinated on the slide, the only such instance among non-epileptics.

E.E.B. (m) : : N/200 no clot - 0.25 : : :  
N/240 clot

A.W.P. (m) : : N/180 no clot - 0.29 : : :  
N/200 clot

W.E. (m) : : N/200 no clot - 0.25 : : :  
N/240 clot

## EPILEPTIC

J.R.H. (m) All mixtures except N/150 agglutinated on slide and could not be drawn into tube.

F.D.H. (m) The last two intermixtures only could be drawn into tube and these did not clot.

H.O.M. (m) Several stabs required before blood flowed sufficiently. All agglutinated on slide before intermixture.



EPILEPTIC (continued)

J.McC. (m) Two only obtained (N/240 and N/280). Neither clotted in tube. On expression into water the small amorphous masses dispersed at once.

A.W. (m) Three weaker solutions only obtained; no clot in tube.

R.B. (m) All agglutinated before intermixture.

R.W. (f) Four dilutions obtained; no clotting in tube.

E.H. (f) Three obtained; slight clot (which sank to bottom of dish and then broke up) formed in N/240 dilution.

M.H. (f) All except N/100 and N/280 agglutinated before intermixture and none could be drawn into tube for observation.

THREE SAMPLES OF AMMONIUM OXALATE DILUTION (N/80, N/180, N/320), TWO OF SODIUM CHLORIDE, TWO OF CALCIUM CHLORIDE AND ONE DROP OF UNMIXED BLOOD.

EPILEPTIC.

A.C.C. (m) All agglutinated on slide. Only a few minute drops of the fluid mixed with air bubbles could be obtained from the base of the drop. If the point of the tube was placed in the middle of the drop and suction applied, the agglutinated mass formed a plug and did not enter the tube.

D.A.W. (m) All ammonium oxalate dilutions, the weaker calcium chloride and the unmixed drop were obtained. No coagulation occurred in ammonium oxalate. In calcium dilution a ~~true~~<sup>thin</sup> retractorile clot formed. The unmixed drop agglutinated and lay along wall of tube.

From the remainder of the cases (5 male and 6 female) I likewise obtained no information regarding the calcium content as in no case did coagulation occur in the ammonium oxalate dilutions. In all the instances (4) in which they were drawn into the tube a true retractile clot formed in the calcium chloride solutions.

In seven instances, out of a total of eight obtained, retractile clots formed in the calcium chloride solutions.

In only one case (C.F.G., m.) did a true clot form in an unmixed drop out of eight obtained.

From these results I make the following deductions-

That an unusual proclivity to agglutination on exposure and on contact with a foreign body exists in epileptic blood. That epileptic blood, except when mixed with fairly strong solutions of the chlorides of calcium and sodium, rarely forms a true strong retractile clot in a capillary tube.

## Appendix D.

Total leucocyte count in 28 cases, taken in interparoxysmal period between 3 and 5 p. m. at least 24 hours from the 'fit zone'.

Initials. Sex. Leucocytes. Blood plates by Bromine Method.

W.G.	M.	9,200	
J.P.B.	M.	13,400	
A.S.	M.	11,200	
J.H.G.	M.	15,800	660,000
J.C.	M.	8,900	186,000
H.O.M.	M.	11,400	254,000
J.McC.	M.	10,600	
C.V.	M.	10,800	
D.A.W.	M.	14,200	980,000
J.R.H.	M.	15,400	
F.T.H.	M.	9,800	
J.L.	M.	10,200	
A.W.	M.	14,800	124,000
R.B.	M.	8,800	730,000
J.B.	M.	12,000	
A.C.G.	M.	11,800	
A.H.	M.	8,600	
E.T.	F.	13,200	396,000
M.B.C.	F.	11,400	
G.M.	F.	9,20½	970,000
E.H.	F.	7,600	
R.W.	F.	14,200	
E.P.R.	F.	8,200	
A.I.H.	F.	9,600	
G.S.	M.	13,400	
E.K.	M.	15,200	
T.C.	M.	8,800	110,000
G.L.	F.	12,400	



Out of eleven differential counts in patients who were having frequent fits, in only three instances was I successful in making a count at an interval not longer than one hour before a convulsion, beyond which limit I did not consider the count could reasonably be termed prepa-roxysmal. In these three instances I managed to draw blood for the postparoxysmal count within ten minutes after the cessation of the clonic spasm. The results of these differential counts shew a relative decrease of polymorphonuclear cells of a varying degree and in all cases an increase in the total leucocyte count.

PREPAROXYSMAL				POSTPAROXYSMAL			
Poly-	Large	Small	Eosino	Poly-	Large	Small	Eosino
nuclears	Lymph-	Lymph-	philes	nuclears	Lympho	Lymph-	philes
G.C. 78%	ocytes	ocytes		ocytes	ocytes		
G.C. 78%	7%	13%	2%	61%	12%	23%	4%
(m)	W.B.C. 9,800			W.B.C. 12,200			
J.McC. 74%	5%	20%	1%	71%	11%	15%	3%
(m)	W.B.C. 11,200			W.B.C. 11,800			
A.W. 69%	8%	21%	2%	61%	6%	28%	5%
(m)	W.B.C. 11,400			W.B.C. 12,400			

The other differential counts shewed no marked abnormalities except an eosinophilia of 7% in one case.

## ESTIMATION OF URINARY CHANGES.

In the examination of the pre- and post-paroxysmal urines on eighteen occasions of grand mal and five occasions of petit mal, the uric acid estimations were made by heating five drops of urine with one drop of pure nitric acid in a white porcelain dish. When evaporation was almost complete a drop of liquor ammonii fortis was placed at the edge of the residue and the absence of change or the intensity of the purplish coloration gave a fair indication of the quantity of uric acid present. In two female post-paroxysmal urines distinct uric acid crystals were visible.

The albumose test was carried out by heating 5 c.c. of urine, filtered if necessary, with ten drops of a saturated solution of picric acid. If the resultant solution was perfectly clear, it was allowed to stand for one hour and then the appearance of distinct cloudiness was taken as a positive reaction. In the cases which I examined by the half and complete saturation with ammonium sulphate test I found both primary and secondary albumoses present. In some cases crystals of uric acid occurred in these positive albumose solutions.

The constant increase in the quantity of mucin passed was very striking. We should expect that changes in the blood and lymph which affect the ~~blood and lymph~~ nucleoprotein should also affect the mucin elements whose solubilities are exactly similar in the body fluids.

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Hutchison and Rainy, Clinical Methods, 1908. Uric Acid, p. 333

Albumose p. 345.

Milroy, Practical Physiological Chemistry, 1904, Saturation Tests  
p. 191.

## CONCLUSIONS:-

In eighteen consecutive examinations of the last urine voided before the convulsive attack and the first voided after the uric acid was in each case increased the albumose was increased in fourteen cases the mucin was increased in seventeen cases

In five cases of petit mal the uric acid was increased in three cases the albumose was increased in three cases the mucin was increased in all

In no case was the quantum of any of the three substances diminished after the attack but the degree of change was less marked in petit mal than in grand mal.



U.A. = URIC ACID.  
A = ALBUMOSE.

M = MUCIN  
SL. SLIGHT.

FIGURES = SPEC. GRAVITY  
REACTION = AC. NEUT. OR ALK.

(M) = MALE  
(F) = FEMALE.

INITIALS	PRE-PAROXYSMAL	POST-PAROXYSMAL	INITIALS	PRE-PAROXYSMAL	POST-PAROXYSMAL	INITIALS	PRE-PAROXYSMAL	POST-PAROXYSMAL
J.R.H.(M)	U.A. - A. - M. SL. AC. 1009.	++ ++ ++ AC. 1014.	A.S.(M)	U.A. - A. - M. - NEUT. 1014	++ SL. ++ AC. 1019	R.W.(F.) (PETIT MAL)	U.A. SL. A. + M. - AC. 1021	++ ++ ++ AC. 1012.
H.G.N.(M)	U.A. SL. A. - M. - AC. 1018	++ - - AC. 1015.	A.C.G.(M)	U.A. - A. - M. - AC. 1010	++ ++ ++ AC. 1011.	M.C.(F.)	U.A. - A. - M. - AC. 1010	++ (CRYSTALS) ++ ++ AC. 1014.
A.T.N.(M)	U.A. - A. - M. - NEUT. 1014.	++ ++ ++ AC. 1017.	E.F.(F.)	U.A. + A. - M. - AC. 1004.	++ (CRYSTALS) - ++ AC. 1011.	F.T.H.(M)	U.A. - A. - M. - NEUT. 1006	++ ++ ++ AC. 1011.
H.C.(M)	U.A. + A. - M. - AC. 1010	++ ++ ++ AC. 1015.	W.G.(M) (PETIT MAL)	U.A. SL. A. - M. SL. AC. 1010	++ - ++ AC. 1016.	H.T.(M)	U.A. - A. SL. M. + AC. 1019.	++ (CRYSTALS) ++ ++ AC. 1014.
A.G.G.(M)	U.A. + A. - M. - NEUT. 1017	++ - ++ AC. 1016.	J.P.B.(M)	U.A. - A. - M. - AC. 1009	++ - ++ AC. 1014.	G.F.G.(M)	U.A. - A. - M. + AC. 1016.	++ ++ ++ AC. 1024.
T.P.(M)	U.A. - A. - M. - AC. 1011	++ ++ ++ AC. 1019.	A.D.(M) (PETIT MAL)	U.A. + A. - M. + AC. 1006.	++ - ++ AC. 1014.	W.G.(M) (PETIT MAL)	U.A. - A. - M. - AC. 1009	SL. - ++ AC. 1016.
J.W.G.(M)	U.A. - A. - M. + AC. 1015.	++ ++ ++ AC. 1012.	A.H.(F) (PETIT MAL)	U.A. SL. A. SL. M. SL. AC. 1009.	SL. ++ ++ AC. 1014.	F.T.H.(M)	U.A. SL. A. - M. - NEUT. 1012.	++ ++ ++ AC. 1020.

## Appendix F.

### Daily Charts of Phosphate Excretion in Two Cases.

The total excretion in both cases was comparatively low. The dietary of an Asylum along with the comparative lack of exercise are the probable causes of this condition. The excretion is greater after the convulsive attacks.

The striking change in the time incidence of the convulsions in H.OpM. followed the substitution on April 1st of a pint of breakfast coffee for a pint of cocoa.

Sanatogen produced a rapid and pronounced deleterious effect on this patient, increasing the number and severity of his attacks. During the time of its exhibition he was in a state of confusion and unable to work.

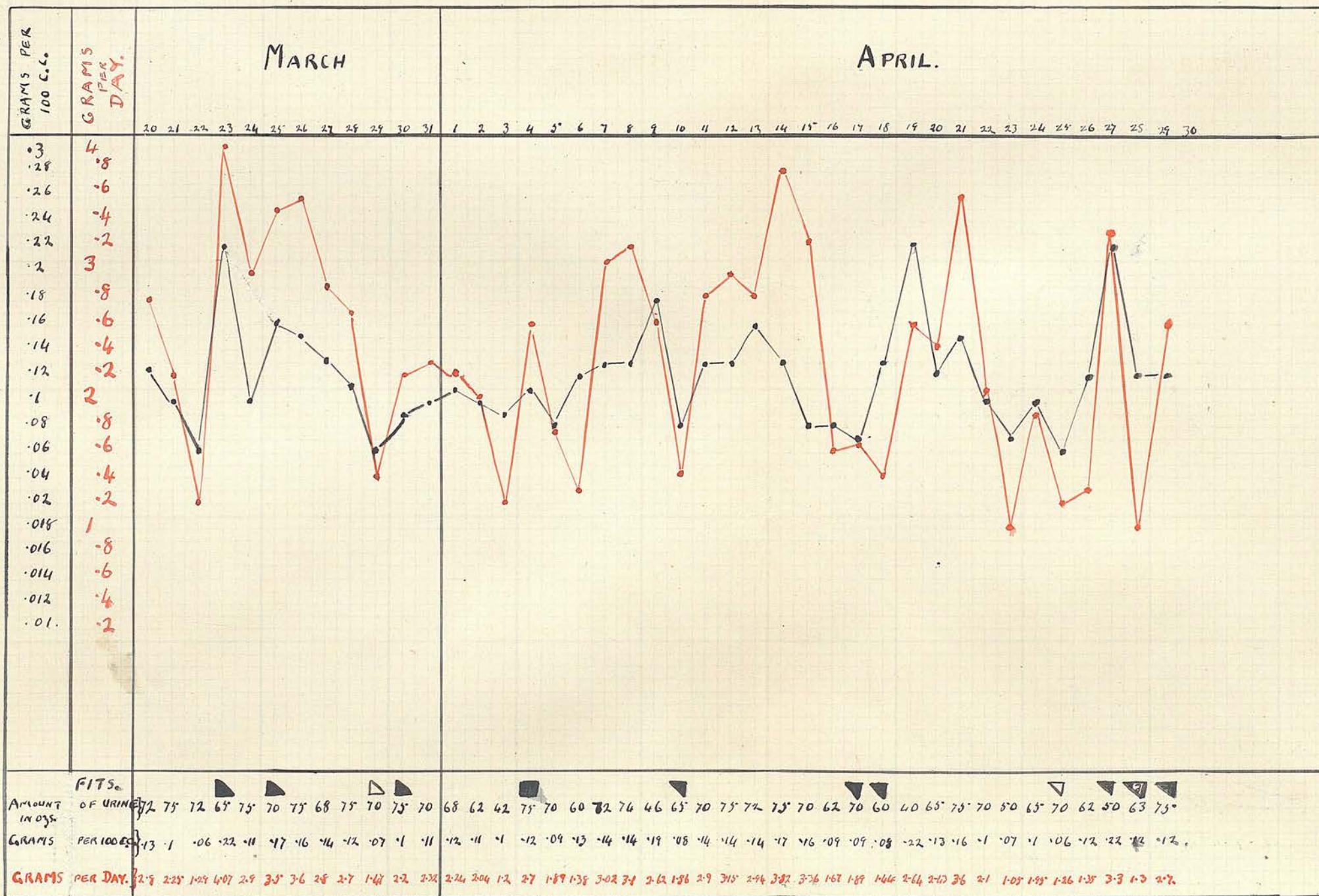
The quantitative phosphate estimations were made by the Uranium Nitrate titration method with tincture of Cochineal as indicator(1).








(1) Hutchison and Rainy, Clinical Methods, p.324.



# PHOSPHATE ESTIMATION [H.O.M.]



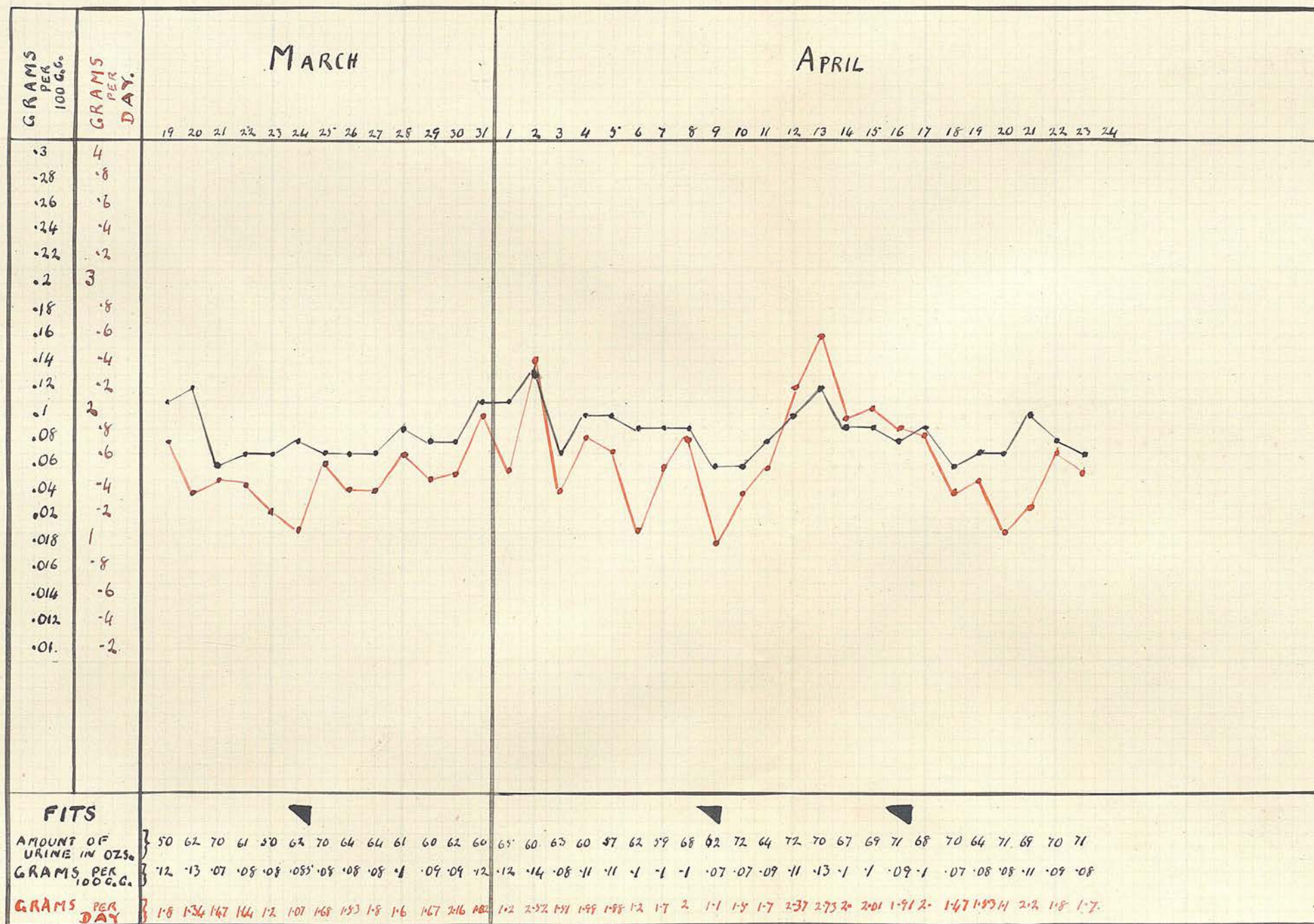
NIGHT FIT =   
 DAY FIT + NIGHT FIT =   
 DAY FIT = 

GRAND MAL =   
 PETIT MAL = 

BLACK LINE = GRAMS PER 100 C.C.  
 RED LINE = GRAMS PER DAY.



# PHOSPHATE ESTIMATION [J.C.]





## Summary of Treatment.

In addition to the bromides of ammonium, sodium and potassium I have observed the effects upon epileptic patients of the following substances:-

Ammonium Oxalate and Oxalic Acid

Calcium Chloride

Calcium Lactate

Calcium Glycerophosphate

Sodium Carbonate and Bicarbonate

Lecithin

Liquor Thyroides

Sanatogen

Phytin Liquidum

Parathyroid Extract (I obtained a small quantity of this substance from Messrs. Allen and Hanbury.

Prescribed en cachet, in 2 grain doses twice a day, it produced no effect in two cases and its cost precluded further observation)

In all the cases which were treated I omitted all medicine except the ordinary institution aperient for at least three weeks in patients who were having frequent fits, and for periods of two or three months in patients who had few fits. No patients whose fits occurred in cycles were chosen for therapeutic investigations as fallacious conclusions of success or failure might have resulted from their irregular manifestations.

4  
From the administration of Oxalic acid and Ammonium oxalate I obtained very good results in 13 out of 15 cases. Their most marked effect lay in the shortening of the post-paroxysmal states of stupor and headache and in the improvement in the patient's mental state in the inter-paroxysmal period. One example of the change in manner of recovery I have already described (p. 25) and in varying degree this effect was observable in all the cases.

In three cases along with a reduction in the total number of paroxysms the minor attacks almost entirely disappeared.

Of the three cases which I consider unsuccessful two were patients who were having infrequent fits which were not inhibited by oxalic acid as could be done by bromide. The third case was speciaally inteleslinu. On large doses of bromide (Ammon. Brom., Pot. Brom., Stront. Brom., aa. gr. 10, t. i. d.) the patient had an average over five months of nine fits per week. When I omitted the bromides he immediately commenced to have a large number of nocturnal fits- from three to six per night- and after five days in this condition I commenced the small dose of oxalic aci. This produced no effect in reducing the number of his attacks in seven days and I was forced to restore the bromides to him. It is now seven weeks since the bromides were restored and his average number of fits is still high compared with his original state on bromide. The attacks in this patient are almost entirely nocturnal in his normal routine but when kept in bed during the day for mental or physical reasons, his postural incidence is shewn by frequent attacks. His nocturnal attacks were not, however, diminished by sleeping in a semi-recumbent position.

The beneficial effects upon two of the cases became less marked after the ~~ex~~piry of five weeks in one instance and seven weeks in another. By the administration of oxalic acid, gr. 1, in the morning and ten grains of bromide in the evening in these two



cases the total number of fits is still much below that of the period in which no medicine was given. I prescribed these substances as follows-

Oxalic acid, gr.½. (or Ammon. oxalat. gr.1.)

Aq. dest. ad ½ oz.

Sig. 4 times a day, 1 hour before meals.

In no case have I observed the slightest ill effects with these doses. My original use of oxalic acid was the result of a conviction that the epileptic manifestations were produced by an agglutinative or coagulative process. From Citric acid I obtained no results and, finding that oxalic acid had been used therapeutically in scurvy, I determined to try it and consider the results very gratifying. Of the two substances I prefer oxalic acid to ammonium oxalate. The immediate recrudescence of the post-paroxysmal symptoms in several cases when these substances were omitted and bromides prescribed has convinced me of their usefulness.

It is highly probable that the oxalic acid acts by inactivation of the calcium of the blood as a coagulative factor. Its presence does not inhibit agglutination in epileptic blood outside the body, as has been shewn in appendix C. I consider it probable that the oxalates may neutralise the excess of calcium which is drawn from the tissues in the markedly hypoalkaline states and so may diminish the tendency to disruption of the polymorph cells which an excess of the ordinary calcium salts in the blood will effect. In this way the earliest factor favouring agglutination, the excess of blood plates, may be counteracted although the addition of the oxalates to the shed blood in which the disruption has already occurred cannot stay agglutination. Cramer and Pringle(1) have shewn that the effect of the oxalates is to keep the blood plates intact and so prevent coagulation. I believe that the rapid recovery after convulsions shewn by patients on the oxalates may

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(1) Cramer and Pringle, Quart. Jour. of Experimental Phys. Feb. 1913, p.5.

be due to the limitation of the blood plates to their mechanical effects in contradistinction to their chemical potentialities.

The exhibition of the Calcium salts produced a slight ~~inc~~ increase in the number of the fits and in some cages a striking change in their character in the way of a marked lengthening of the preconvulsive stage of twitching and rigidity. It is probable that the comparatively slight effects produced by calcium are due to the difficulty, as Addis has demonstrated, of raising the calcium content of the blood by therapeutic means. I prescribed calcium as follows:-

R. Calc. Chlor. gr. 20 (or Calc. Lactat. gr.20k  
Aq. ad 1 oz. T.i.d.

r. Calc. Glycerophosphat. gr. 20  
Aq. aurant. ad 1 oz. B.i.d.

From the alkalies (Sod. carb. or bicarb. gr.25, T.i.d.) I obtained very good results, the number of fits being in some cases considerably reduced and the mental state improved. Glycerine of Lecithin (drachms 2, b.i.d.) had no marked effect nor had Liquor Thyroidei, m.10, T.i.u.

Sanatogen (drachm 1, b.i.d.) and to a less degree Phytin Liquidum (a vegetable preparation containing calcium and magnesium phosphate with diphosphoric acid) (drachm ½, t.i.d.) produced a definite increase in the number and severity of the convulsions.

From these results I conclude that a slightly greater degree of vaso-motor instability exists among epileptics than among non-epileptics.

In these charts a general impression is sought of the relative stability of the vaso-motor system in epileptic and non-epileptic subjects.

The charts shew-

Heart. A - sign indicates the presence of slight cardiac symptoms of shortness of breath on exertion, palpitation, cardiovascular oedema of the feet or irregularity in the rhythm of the pulse. No severe cardiac cases with epilepsy are at present in this institution.

Blood Vessels. A - sign signifies palpable thickening of the arterial walls.

Blood Pressure. The maximum systolic pressure taken between 3 and 5 P.M.

Pulse Mobility. Three observations on the pulse rate of patients were taken before and after rising on consecutive mornings by the trained staff at my request. I have taken the average of these results in each case to estimate the pulse mobility.

Tache Cerebrale. As the criterion of the presence of tache cerebrale I took distinct visibility at a distance of 6 feet

Capillary Pulsation. In all the cases I examined the mucous membrane of the inner side of the lower lip by pressing lightly with a glass slide: - indicates a visible pulsation.

I also made enquiries in all these cases regarding sleep and any pronounced tendency to dreams. Even if the statements of the patients were reliable the results were not of great importance. From the statements of the staff the soundness of sleep appears to be slightly greater among epileptics than among non-epileptics.

From these results I conclude that a slightly greater degree of vaso-motor instability exists among epileptics than among non-epileptics,

that in a few isolated cases



this instability may be an accessory cause of a convulsion,  
that the degree of instability is  
much less than may be seen in many non-convulsive conditions, e.g.  
exophthalmic goitre and some central nervous lesions,

that, with the exception of the  
grave circulatory disorder in the Stokes Adams syndrome, vaso-  
motor instability is inadequate and unproven as a cause of  
epileptic manifestations.



INITIALS	SEX	AGE	EPILEPTIC OR NON-EPILEPTIC	HEART	BLOOD VESSELS	BLOOD PRESSURE.	PULSE MOBILITY					TACHE CÉRÉBRALE	CAPILLARY PULSATION.
							BEFORE RISING	AVERAGE	AFTER RISING	AVERAGE	DIFFERENCE.		
A.W.	M.	32	EPILEPTIC	0	+ SLIGHT.	195	51 50 53	52	59 65 66	63	11.	—	—
R.B.	"	66	"	0	+ SL.	135	61 55 56	57	60 70 68	69	12	—	—
J.R.H.	"	18.	"	0	—	117	63 71 70	68	88 93 87	89	21	—	—
A.C.G.	"	26	"	0	—	142	74 66 60	67	78 89 77	81	14	—	—
C.V.	"	23.	"	0	—	135	51 55 50	52	52 59 53	55.	3	—	—
D.A.W.	"	36	"	0	—	122	61 66 70	66	86 80 80	86	20	—	—
W.G.	"	39	"	0	—	140	61 64 67	64	87 90 99	92	28	+	—
J.L.	"	51	"	+	+	138	72 72 74	73	97 100 103	101	28	+	—
J.H.B.	"	65	"	+	+	220	87 75 80	81	106 82 88	92	11	—	—
A.S.	"	22	"	+ MITRAL INCOMP. RETENCE.	—	135	93 87 90	90	127 117 120	122	32	+	—
J.B.	"	79	"	+	+	148	85 87 86	86	95 98 101	98	12	—	—
G.F.G.	"	23	"	0	—	130	52 52 50	51	82 94 99	93	42	—	—



INITIALS.	SEX	AGE	EPILEPTIC OR NON-EPILEPTIC	HEART.	BLOOD VESSELS	BLOOD PRESSURE.	PULSE		MOBILITY.		DIFFERENCE	TACHE CÉRÉBRALE	CAPILLARY PULSATION
							BEFORE RISING	AVERAGE	AFTER RISING	AVERAGE			
A.D.	M.	36	EPILEPTIC	0	+ SLIGHT	109	66 60 61	62	82 76 74	77	15	+	—
J.P.B.	"	49.	"	0	+ SL.	140	71 77 74	74	99 96 83	93	19	—	—
F.T.H.	"	43.	"	0	—	145	71 72 81	75	90 88 102	93	18	—	—
J.M.E.C.	"	72	"	+	+	145	68 75 61	68	84 84 80	83	15	+	—
H.O.M.	"	34	"	0	—	143.	71 74 59	68	90 87 77	85	17	—	—
J.E.	"	46	"	0	+	152	68 80 72	73	71 84 79	78	5	—	—
A.H.	"	48	"	+	—	149	71 74 74	75	101 111 96	104	29	+	—
R.W.	F.	20	"	0	—	140	87 66 77	77	91 80 75	82	5	+	—
E.H.	"	23.	"	0	—	145	59 74 63	65	78 80 71	79	14	+	—
A.I.H.	"	37	"	0	—	160	71 79 74	75	87 91 88	89	14	—	—
M.B.C.	"	39	"	0	—	145.	59 53 60	57	91 92 99	94	37	—	—
E.T.	"	26	"	0	—	125	86 79 81	82	84 86 90	90	8	—	—
E.R.	"	54	"	+	—	155	72 76 74	74	89 96 91	92	18	—	—



INITIALS	SEX	AGE	EPILEPTIC OR NON-EPILEPTIC	HEART	BLOOD VESSELS	BLOOD PRESSURE.	PULSE MOBILITY.					TACHE CÉRÉBRALE	CAPILLARY PULSATION.
							BEFORE RISING.	AVERAGE	AFTER RISING.	AVERAGE.	DIFFERENCE		
E. H.	F	20	EPILEPTIC	0	-	135°	74 } 80 } 80 }	78	89 } 86 } 89 }	96	18	-	-
G. M.	"	32	"	0	+SL.	130	64 } 69 } 63 }	65	80 } 89 } 91 }	90	25	+SL.	-
M. S.	"	19	NON- EPILEPTIC	0	+SL.	110	75 } 65 } 62 }	71	87 } 82 } 79 }	83	12	-	-
A. B.	"	36	"	0	-	154	78 } 76 } 72 }	75	81 } 85 } 82 }	83	8	-	-
M. A. E. B.	"	21	"	0	-	140	55 } 81 } 80 }	72	68 } 86 } 81 }	78	6	-	-
F. A. D.	"	22	"	0	-	140	73 } 74 } 71 }	73	77 } 83 } 77 }	79	6	+SL.	-
S. D.	"	49	"	0	+SL.	155°	89 } 59 } 60 }	69	98 } 80 } 90 }	89	20	-	-
E. R.	"	49	"	0	-	165°	82 } 84 } 80 }	82	107 } 101 } 102 }	103	21	++	-
W. G.	M	45	"	0	-	118	69 } 73 } 70 }	71	86 } 86 } 82 }	85	14	-	SL.
E. C.	"	46	"	0	-	212	85 } 76 } 77 }	78	97 } 93 } 85 }	92	14	-	-
H. T.	"	40	"	0	-	120.	79 } 72 } 69 }	73.	96 } 84 } 88 }	89	16.	-	-



# Quantitative Estimation of Nucleoprotein, Ether soluble substances and Brominated Nucleoprotein.

In making these estimations I early perceived that, with the means at my disposal, the attainment of a high degree of accuracy in the results was not possible and I have intentionally refrained from basing any deductions affecting the general trend of my thesis upon them. In the specimens of brain which I took for maceration the relative proportion of white and gray matter cannot have been constant, and the method of preparation of nucleoprotein generally employed does not altogether exclude the contamination of other soluble proteins. The only points in these investigations of which I have felt entitled to make use are the solubility and insolubility of the nucleoproteins upon a very slight divergence from neutrality of the solvent and the effect of bromine in producing a precipitate which contained phosphorus from a nucleoproteid solution.

For the tabulated results therefore, although obtained by careful measurements and uniform methods, nothing more is claimed than a comparative value.

The results quoted represent:-

1. The quantity of precipitated nucleoprotein obtained from 70 c.c. of a 100 c.c. mixture of sodium carbonate solution with 16 grammes of brain substance (46 cases).
2. The quantity of the bromination precipitate in duplicate solutions to those of No.1. (26 cases ).
3. The quantity of ether soluble substances (chiefly lecithin) in the same amount of brain substance (46 cases)

The acetic acid and bromine precipitates are estimated by their bulk in c.c. upon centrifugalisation after sedimentation for 24 hours in a long graduated tube. The lecithin figures represent weight in grammes for 16 grammes of brain substance. An attempt to precipitate the lecithin from the ethereal solution for estimation

by adding acetone was useless owing to the firm adherence of the particles to the sides of the long tubes.

In proving the presence of phosphorus, which I did in 37 nucleoproteid precipitates by acetic acid, all the bromine precipitates and 32 lecithins, I also estimated its amount by centrifuging the white precipitate of ammonio-magnesium phosphate. The amounts were too small to dry and weigh with any accuracy but by the centrifuge I found that the quantity bore a fairly constant ratio to the amount of nucleoproteid and lecithin.

#### Brain Substance.

Remove a slice weighing about 60 grammes from the right cerebral vertex, having thoroughly stripped the membranes. Reduce it to pulp within 36 hours after death by pounding and pressing through a glass filter funnel with a glass plunger.

#### Preparation of Nucleoprotein.

Weigh out 16 grammes of pulp and place it in a glass cup. Add 100 c.c.s of aqueous sod. carb. solution (1.5%). Stir thoroughly with glass rod and allow mixture to stand for 24 hours. Filter through coarse and fine filter paper and precipitate by adding ~~200~~ about 6 c.c. acetic acid (1%). Allow to stand for 24 hours and then redissolve in .5% sodium hydroxide from which precipitate again by acetic acid. The amount of solution which would pass through the filter papers varied in different cases owing to differences in viscosity and I was compelled to adopt the standard of 70 c.c. as the quantity from which I proceeded to take a precipitate.

#### Estimation of Phosphorus in Nucleoprotein.

Remove water from above precipitate and partially dry remainder in crucible without charring. To this add and intermix about ten times its bulk of potassium nitrate and sodium carbonate mixture (2 parts of pot. nitrat. to 1 of sod. carb. thoroughly mixed) and incinerate. The mass turns black and, if heated too rapidly,



crackles and sparks. When a hard white cake forms at the bottom of the crucible and no black particles remain, add the minimal quantity of water which will dissolve it (slight heating may be required).

Drive off  $\text{C.O}_2$  with a small quantity of pure  $\text{H.Cl.}$  using a pipette and neutralise by adding Liq. Ammon. Fort. Filter solution and add about half its bulk of magnesia mixture in the long tube. Shake for two minutes and allow to stand for 24 hours. Remove most of the fluid over precipitate, agitate and pour fluid with precipitate into centrifuge tube.

#### Lecithin.

Place similar quantity of pulp in glass cup and add 64 c.c.s of methylated ether. Allow to stand for 48 hours, stirring several times, and filter into glass bottle. Allow bottle to remain uncorked (a filmy deposit will appear) until contents can be poured into crucible. Allow further evaporation to proceed until semi-solid (about 48 hours) and complete process on water bath.

Phosphorus estimation from lecithin is similar to that from nucleoprotein, the incineration mixture and the viscous lecithin being thoroughly mixed.

The process of bromination I have already described and the method of determining the phosphorus content is the same as in the nucleoprotein precipitate by acetic acid. 35 c.c.s of the sod. carb. solution ~~was~~ taken and the acetic acid precipitate dissolved in alkali before being placed in the Soxhlet tube for bromination. The resultant precipitate has been doubled to give corresponding results.



FORM OF INSANITY.	INITIALS	SEX.	NUCLEOPROTEIN PRECIPITATED BY ACETIC ACID.	NUCLEOPROTEIN PRECIPITATED BY BROMINE.	LECITHIN (GRAMMES)	FORM OF INSANITY.	INITIALS	SEX	NUCLEOPROTEIN PRECIPITATED BY ACETIC ACID.	NUCLEOPROTEIN PRECIPITATED BY BROMINE.	LECITHIN (GRAMMES).
			CUBIC CENTIMETRES.	CUBIC CENTIMETRES.					C.C.,	C.C.,	
EPILEPSY.	W.T.	M.	2.2		.9	DEMENTIA	A.W.C.	M	5.9		1.15
"	W.S.	"	4.2	4.3	1.32	WITH MARKED WASTING OF BRAIN	J.W.	"	3.1		.92
"	F.K.	F.	4.3	4.8	1.1	"	W.T.D.	"	.9		.86
"	B.F.	"	3.8	3.6	.995	"	M.R.	F	3.2	3.7	.75
"	J.A.	"	3.4.	3.9.	.74.	"	M.D.B.	"	1.8	1.9	.97
						"	T.G.	M.	2.4.	2.6.	.61
GENERAL PARALYSIS OF INSANE.	F.D.	M.	6.9		1.15	IMBECILITY	L.T.	F	(OPALESCENCE	BUT NO PPT.)	.78
"	G.A.	"	2.8	3.1	.82	"	A.M.	"	1.9	2.2	.92
"	H.S.	"	2.9	2.7	1.08						
"	E.P.	"	1.4	1.5	.45	MELANCHOLIA.	E.F.	F.	1.1		.8
"	J.B.	"	3.4	3.2	.62	NO GROSS LESION OR MARKED WASTING.	E.H.	"	1.8		.5
"	T.G.	"	4.1	4.	.65		A.D.	"	5.1		1.1
"	C.S.	"	3.2	3.4.	.61		A.M.S.	"	6.1	6.6	1.01
"	E.W.	F.	4.1		1.1		E.M.	"	2.4	2.4	.65
"	H.E.H.	"	6.1		1.14		E.R.	"	4.3	4.6	.73
"	R.E.F.	"	3.8	3.9	.95		E.P.	M	3.3.		.92
							C.D.B.	"	5.2		.72
ORGANIC BRAIN DISEASE.	W.T.F.	M.	5.	5.1	.7		C.D.	"	2.	1.9	1.2
"	A.T.	"	3.8	4.2	.92						
"	E.B.	F	5.2		.44						
"	J.H.	"	4.1	4.1	1.02	CHRONIC MANIA.	E.M.H.	F.	3.1		.48
"	C.D.	"	4.5.	4.7	.41						
DELUSIONAL INSANITY	L.P.M.	M.	4.7		1.1		* BABY L.	M.	3.4	4.1	.32
	W.L.	"	5.1		.56		Brain of 3 weeks in hand, Mother present when certified.				
	E.M.H.	F.	4.9		1.2.						
	C.F.	"	5.1		.75						
	S.H.	"	4.2		.85						
	L.M.S.	"	2.2	2.7	.78						
	A.T.B.	"	4.5.	4.4.	.8.						



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